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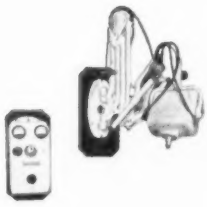

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4. Trafton, H. M., and Lind, H. E.: J. Urol. 69:315 (Feb.) 1953.

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Determination of Tyrosinase Activity in Micro-Quantities of Tissue Using Radioactive C14 Labeled Tyrosine. Atsushi Kukita, M.D., Thomas B. Fitzpatrick, M.D., Ph.D., and Aaron B. Lerner, M.D., Ph.D.

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Technic of Assay of an Unknown Steroid for Possible Local Activity in the Skin of Man. Leon Goldman, M.D., Richard Flatt, M.D., and Jeanne Baskett, B.S.

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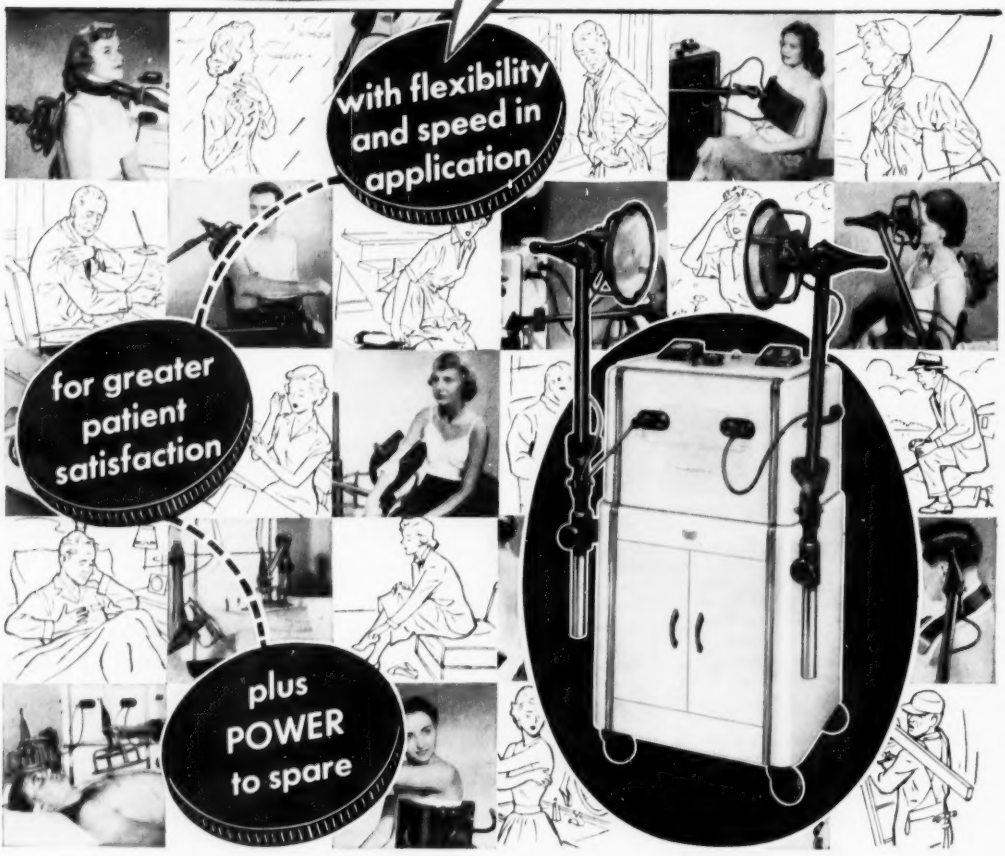

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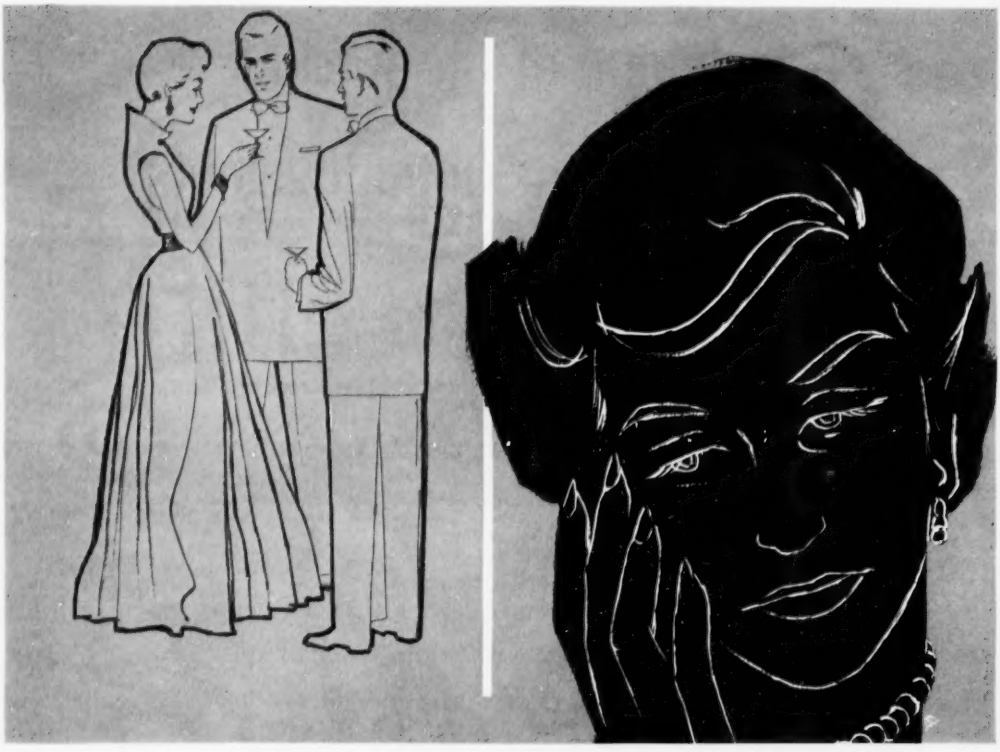

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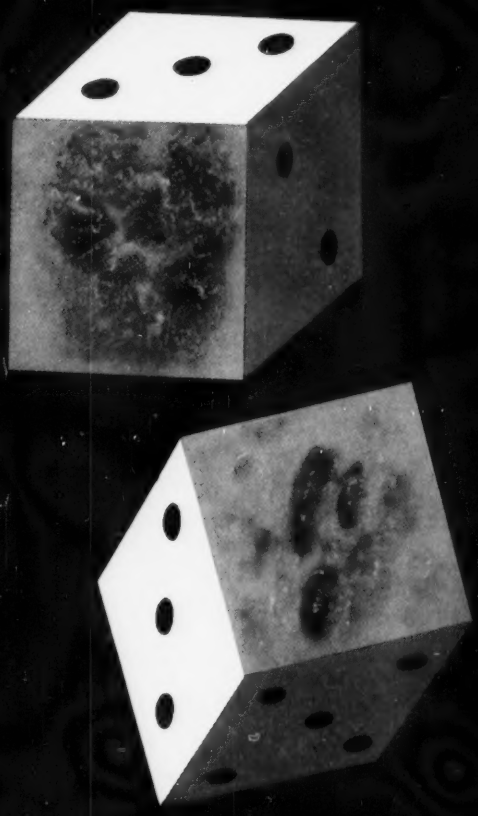

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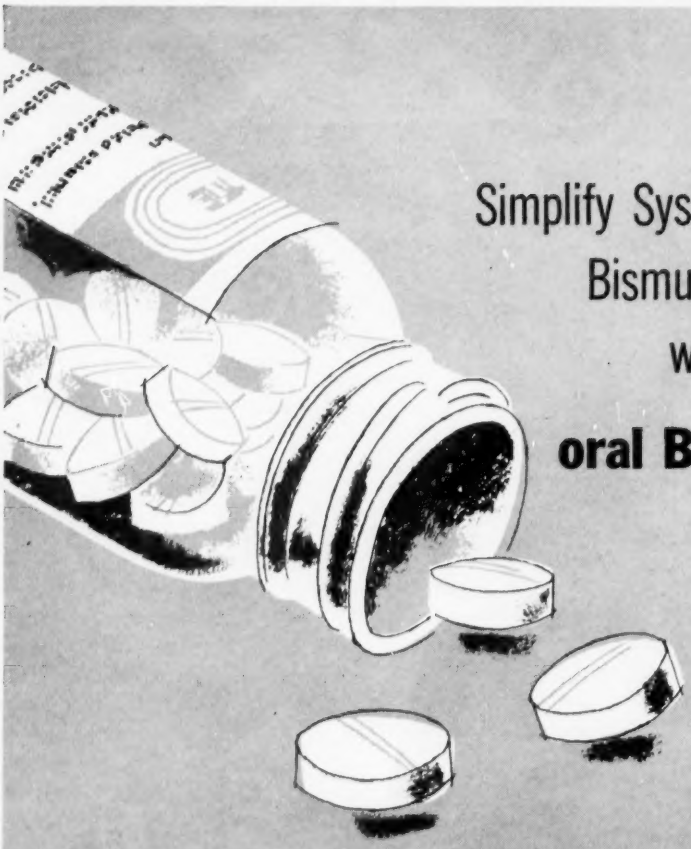

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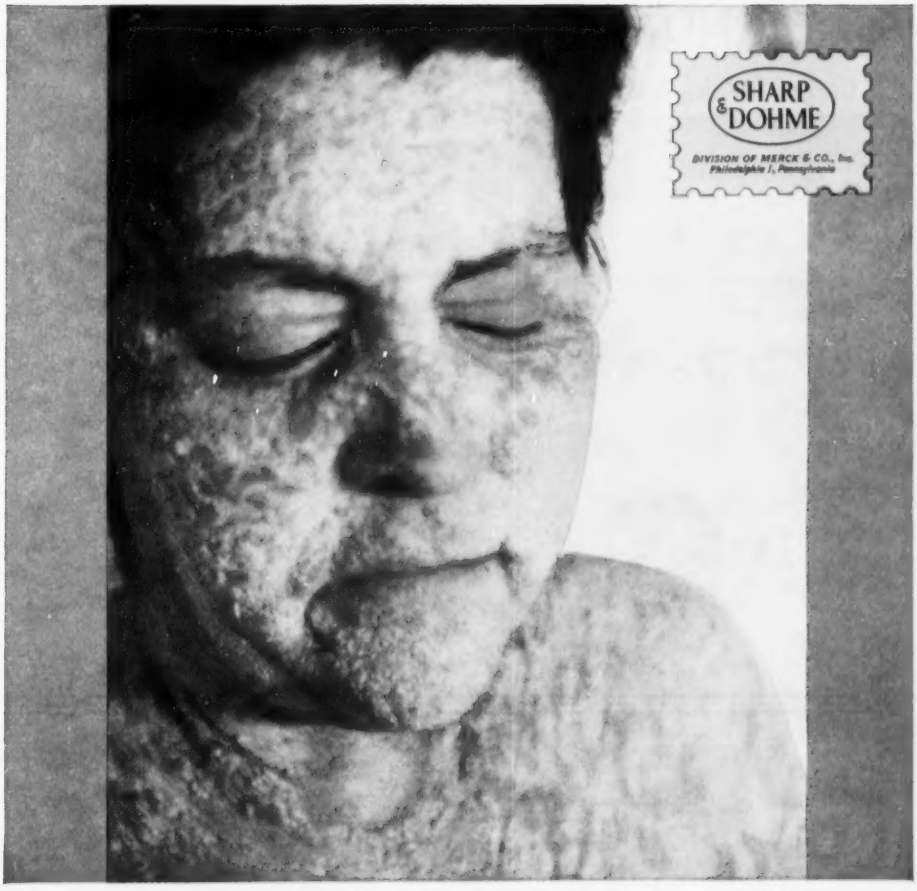

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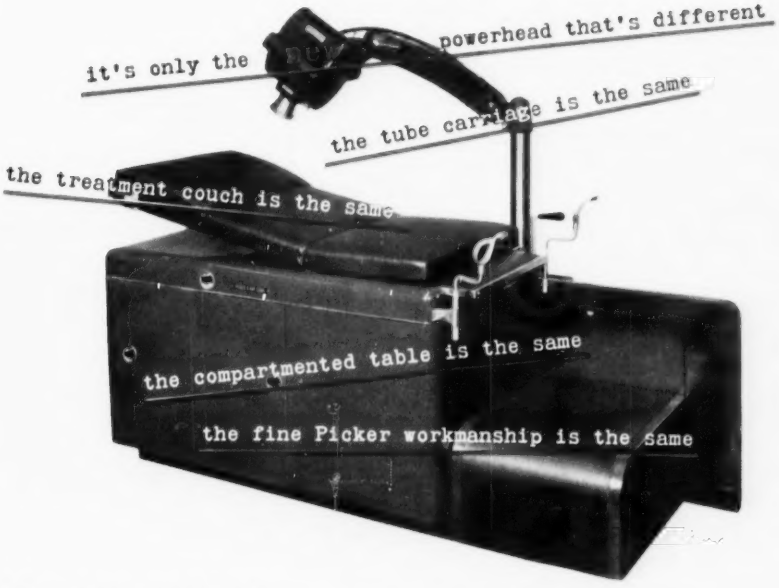
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EVALUATION OF DERMAL SENSITIVITY

Animal and Human Tests Compared

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DURING the past few years there has been a growing demand for more effective or more extensive pretesting of cosmetics and dermal pharmaceutical products, not only because of the increased use of newer ingredients, but also because in several recent instances, products apparently adequately tested by present prophetic methods have been found to be dermal sensitizers under use conditions. The publicity given these untoward reactions has resulted in Congressional Committee investigation, the recommendations from which have been for further extension of federal regulatory legislation. Such mandatory requirements for complete pretesting of cosmetic materials would be entirely in order if it were assured that the testing methods were reliable. That this has not been the case is illustrated by the beforementioned method failures, namely, products such as the nail polish undercoat and quaternary shampoos which showed themselves to be dangerous under use conditions. Arbitrary proposals to extend and elaborate on present methods * without offering reasonable assurance that the new methods will be more satisfactory (i. e., more prophetic) than the old are unrealistic and uneconomic. Through comparative study of various dermal formulations with several irritation-sensitivity testing methods, we have developed a prophetic test which we feel utilizes the advantages and simplicity of the older methods, yet extends the prophetic reliability of the test into conditions of actual use. In this study we are reporting a comparison between animal testing, conventional human prophetic patch testing, and our use test evaluation method upon six typical dermal preparations, three lotions and three ointments.

There are three conventional methods for testing dermal products for their irritation and sensitization potential. The first of these is the rabbit conjunctival sac irritation technique, used routinely in toxicology. For quite a number of years materials having potential industrial hazard have been "screened" on the basis of their irritant potential for eyes. Various attempts have been made to standardize the criteria for evaluating the type and degree of irritation produced. Recently there

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From New York Medical College, Department of Dermatology (Drs. Traub and Spoor); Hazleton Laboratories, Falls Church, Va. (Dr. Tusing).

* Personal communication to the authors (Guinea Pig Test Adaptation to Man).

has been renewed interest in the methods as they apply to cosmetic preparations and to an evaluation of the potential hazard of cosmetics to the public. The method serves its greatest usefulness for preformulation "screening" of ingredients because, in general, the rabbit conjunctiva is far less sensitive than is the skin. Therefore completed formulae which are able to pass the eye test fail on skin testing. The criteria used to measure eye irritation are arbitrary and must measure both the capacity to produce injury and also the potency of this activity. Accepted criteria for measurement of eye irritation are

1. Erythema and edema of the eyelid
2. Erythema and edema of the nictitating membrane
3. Lacrimation
4. Signs of pain response
5. Incidence of opacity
6. Incidence of vascularization of the sclera and cornea

These rabbit eye responses are graded from normal, through mild irritation, moderate irritation, to severe irritation with pannus. The injury criteria are also weighted in terms of duration and severity of the residual pathology.

The second method of testing, also an animal test, is the repeated intradermal insult guinea pig test of Landsteiner and Jacobs (known also as the Draize test of the Pharmacology Division of the Food and Drug Administration). Here the animal receives an intradermal injection of the test substance in appropriate dilution every other day for 10 injections, or a period of 21 days. Then three weeks later a challenge injection at the same site is given. Responses are measured in terms of erythema, induration, and vesiculation, as one would in human testing. There are fundamental differences between human and animal skin. In general, the animal skin lacks sweat glands and has a much greater number of hairs, hair follicles, and sebaceous glands. Less objective is the observation made some years ago that the response of an animal skin, to even the same material, is not as consistent as is that of human skin. In fact, variation in the diet may greatly effect the skin reactivity of an animal. These inconsistencies are particularly evident when patches of test substances are applied to the skin, and it is for this reason that intradermal injection is the method of choice. Histologically the responses elicited by an irritant are comparable with those seen on human skin. The range obtained is from the normal through severe vesicular change.

The third test method, namely, the Schwartz-Peck prophetic patch on human subjects, is too well known among dermatologists to require much discussion here. Suffice it to say that the test requires that a closed patch be applied for 48 hours. Readings of erythema, induration, and vesiculation are made at intervals after removal. Two weeks later the patches are repeated at approximately the same sites, and again dermal response readings are made. As originally proposed this test used as control a preparation of similar type which had been in use for a number of years and which had caused no unusual number of complaints. Schwartz and Peck also recommended comparative use tests as the final means of evaluating products which had satisfactorily passed the patch test. This latter phase of prophetic testing has been deemphasized in practice.

Because of the apparent failure, at times, of these tests to accurately predict potential damage to the public, it has been proposed that the elaborate animal intra-

dermal test be carried over to the human and adopted as a patch-testing technique. The proposal is unrealistic because there is no proof that animal testing and human testing are equivalent, and, even more important, the costs involved and the dangers to be encountered in subjecting humans to so frequent and severe a dermal insult make it prohibitive.

Untoward sensitization reactions to dermal pharmaceutical materials appear during their use; therefore it seemed to us that any method for truly predicting the sensitization potential of a product would demand that the test mimic actual use conditions as closely as practical. Upon this premise, one can postulate that the animal and human prophetic tests fail to accurately predict all unfavorable reactions because they do not test the product either in the particular areas of the skin or on the particular individuals for whom the products are indicated. In our opinion, rather than elaborate on either laboratory or human patch-test techniques, we might

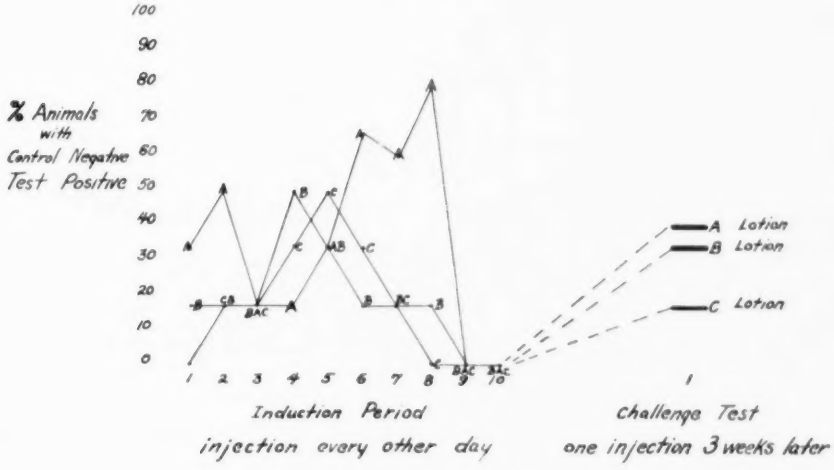

Fig. 1.—Landsteiner-Draize guinea pig intradermal test of lotions.

do well to combine the well-known prophetic patch test with an adequate daily use test. The periods of study can be extended to the lengths recommended by the animal test experts without subjecting humans to either unnecessary manipulation or risks. Testing this thesis, we have studied a number of presumably bland dermal preparations by direct comparison of the animal intradermal, the human prophetic patch, and the use test. The following data show irritation and sensitivity reaction predicting ability of the several methods for the group of products tested.

We studied three lotions, A, B, and C; and three ointments, X, Y, and Z. Lotion A was a bland gum base alkaline emulsified type of cosmetic hand preparation; Lotion B was a nongum base, acid side quaternary emulsified hand preparation, and Lotion C was an ethically marketed non-calamine-containing antihistaminic emulsion. Ointment X was a cosmetic deodorant material containing large quantities of zinc oxide in a petrolatum base. Ointment Y was an acne cream containing elemental sulfur and resorcinol as its active ingredients. Ointment Z was petrolatum containing an organic sulfur analogue of formic acid ester as its therapeutic ingredient.

The rabbit conjunctival irritation test was not sufficiently sensitive to detect appreciable differences among the members of this series; therefore the first animal study to be reported was the intradermal guinea pig test. A modified Landsteiner technique was used. Aqueous 0.1% solutions of the lotions and 0.1% corn-oil solutions of the ointments were prepared. The abdominal fur was clipped from each side of the albino guinea pig test animals. A 0.05 cc. dose of the respective 0.1% solution of test material was injected intracutaneously by means of a 26-gauge needle. A separate group of six guinea pigs was used for each material, and each animal was given an injection every other day until a total of 10 injections had been made. The test injections were made on the left side of each animal. Control injections of 0.05 cc. of distilled water or corn oil were made on the right side of each animal in the same manner as the test materials. Readings were made 48 hours after each of the

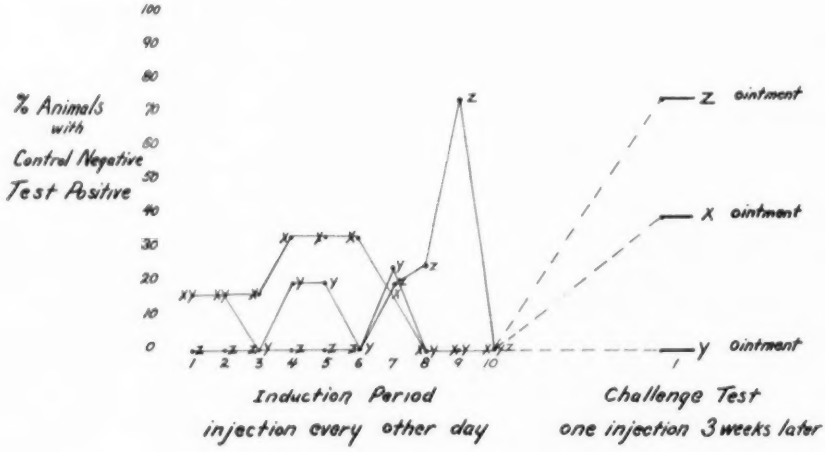

Fig. 2.—Landsteiner-Draize guinea pig intradermal test of ointments.

first 10 injections. Three weeks after the 10th injection, a challenge injection of 0.05 cc. of the test material and 0.05 cc. of the corresponding control carrier, distilled water or corn oil, was given to each animal. Readings were made after 24 and 48 hours. Figure 1 shows the response pattern. The percentage of the animals whose control injection was negative at the time the test injection was positive has been plotted against the injection period. Lotion A, presumably the blandest of the three, showed a trend toward induced irritation. However, the low level of response to the challenge test is interpreted as negative sensitization in all cases. The next figure (Fig. 2) shows the same guinea pig intradermal test with the ointment series. Very little irritation was experienced, although Ointment Z does show some increase with repetition of the injections. In terms of sensitization, the challenge test of Ointment Z was interpreted as suspect sensitizer. Results such as these are only indicative and should be confirmed through use of many more animals. Of the 36 animals used in this study, 6 died during the six-week test period. This figure is

low compared with that which would obtain if more than one test material had been used on each animal or under animal care and diet conditions less ideal than those of our associates.

After the animal tests, each of the six products was given a prophetic patch test by the technique of Schwartz and Peck. Two hundred persons were used for each series, but there was some overlap. For example, Lotions A and B, and Ointment X were studied on one group. Lotion C and Ointment Z on another, and Ointment Y on the third group of persons. For presentation in Table 1 the grades of positive closed patch response have been lumped into two groups, (1) erythema with indura-

TABLE 1.—*Schwartz-Peck Prophetic Patch Test on Humans (200 Subjects)*

	Percentage Response						
	Initial				Challenge		
Lotions	A	B	C		A	B	C
Erythema with induration	0	2	4	(2-wk. interim)	1	0	2
Erythema without induration	25	46	31	(2-wk. interim)	8	17	23
Ointments	X	Y	Z		X	Y	Z
Erythema with induration	2	11	3	(2-wk. interim)	1	12	0
Erythema without induration	16	20	6	(2-wk. interim)	13	19	10

TABLE 2.—*Traub-Spoor Patch and Use Test on Humans*

Test Material	No. and Type of Subjects	Initial Patch, % Positive	Reactions, 3-Week Use	Challenge Patch, % Positive
Lotion A	74 Normals	1.5	1 Vesicular irritation 1 Mild erythema of hands, arms	0
Lotion B	76 Normals	3.0	2 Erythema and dryness of hands, wrists	0
Lotion C	81 Clinical dermatologic	15.0	1 Erythema and pruritis 2 Vesicular reaction 3 Infections secondary to occlusion	12.0
Ointment X	50 Normals 14 Known reactors to X	2.0 7.0	2 Axillary adenopathy 4 Axillary adenopathy 3 Irritation of axillae	0 14.0
Ointment Y	100 Acne	10.0	3 Irritation and aggravation of condition	12.0
Ointment Z	71 Seborrhea and acne	1.4	19 Flare-up of lesions	12.5

tion and (2) erythema without induration. The first category are those considered as 2 + or 3 + or greater; the second category those graded ± or 1 +. Patch test responses indicated very slight primary irritation from the lotions but no suspect sensitization reaction. The ointments also gave little indication of potential sensitization, although Ointment Y, the sulfur and resorcin cream, was quite an irritant under the closed patch. According to this test all materials studied were considered safe for normal use.

Our next comparison was the combined patch and use test. The study periods were first, an initial patch; second, a three-week use test, and finally, a challenge patch two weeks after cessation of use. The use of each product followed its indications; therefore the cosmetic preparations were used on normal-skinned persons, the therapeutic preparations on dermatologic subjects. Table 2 shows our findings in this series. The first column identifies the test material and the second column the

number and type of subjects. The third column shows the results of an initial patch test. Lotion C and Ointment Y containing 1% phenol and 2% resorcin, respectively, again had a relatively high irritation frequency. The next, and most important column, shows the reactions observed during use. Of particular note are the 19 individuals of the 71 given Ointment Z who showed exacerbations of their lesions while using the ointment. Known reactors to the deodorant Ointment X also showed a high incidence of poor tolerance. The challenge patch column gives the percentage reactions observed two weeks after the use trial had ended. Here the responses of Lotion C and Ointment Y were comparable with those of their initial patch. The known reactors to the deodorant showed an increased sensitivity after use, as was anticipated. The most impressive finding was the patch confirmation of the sensitization potential of Ointment Z, the organic-sulfur-containing product. Here an incidence of 12.5% following an initial irritation of 1.4% clearly indicates potential trouble.

SUMMARY

We have studied a number of dermal preparations by both the animal and the human irritation-sensitization evaluation techniques and compared the reaction rate predictions so obtained with that we have obtained with the same preparations under controlled use tests. By combining a product use test with the Schwartz-Peck prophetic patch series in the same subjects we have designed an irritation-sensitization testing technique which not only predicts the likely incidence of dermal reactions from use of the product, but also supplies repeated prolonged contact exposure comparable in frequency with that of the guinea pig intradermal test without the extreme conditions that the adaptation of the animal test to the human would entail.

ABSTRACT OF DISCUSSION

DR. S. M. PECK, New York: I wish to thank the authors for the privilege of discussing their timely and well-thought-out paper.

There is increasing emphasis both by government and manufacturers on "prophetic testing," before a product is put on the market. It is important, therefore, that before a great deal of time and money are spent on any such product that we have a firm basis in believing that we can predict fairly accurately within limits the probable irritating and sensitizing potentials of any new product or chemical so tested.

It is generally agreed that the greater the number of human test subjects used in our experiments the less the factor of error in drawing any conclusions. However, since with the increase in the numbers of the test panel there is a rapidly mounting cost, it is important for us to establish the minimum number of subjects necessary to give us some basic prognostic data. To a certain extent the number of subjects used will depend on the chemicals and materials tested. However, in comparing modifications of a formula concerning which the question of primary irritation comes up, 100 subjects are sufficient. In the use of entirely new chemicals or formulas in which the question of the sensitizing index is to be brought out, a minimum of 200 subjects gives us more reliable information than 100. It must be emphasized that it is almost essential to have a statistician as one of the testing team in the role of a consultant, especially if smaller numbers of subjects are used and minimal reactions both in degree and numbers are to be evaluated.

I agree with the authors that animals must be used in evaluating new chemicals. Animal experiments are necessary to determine toxicity, especially the effects on internal organs. Animal experiments cannot be relied upon to give proper information concerning sensitization and in many instances even as to primary irritation of particular and minimal nature.

It seems to me that the question of sensitization has been stressed too greatly and the factor of primary irritation and interference with normal physiologic function of the skin has been

overlooked in the evaluation of new products. Many chemicals exert only minimal effects which become evident after relatively long application. These effects are due to the interference with normal physiologic function of the skin and in most instances become evident only when human test subjects are employed.

One but has to refer to the unusual toxicity exhibited by penicillin for guinea pigs to illustrate the point that one species of animal is not sufficient to conduct toxicity tests. If we had relied on the guinea pig alone in evaluating the toxic properties of penicillin, this chemotherapeutic agent might never have been put to clinical use. The evaluation of adhesive-tape dermatitis, which in most instances is not due to sensitization, could not have been carried out in animal experiments. Along the same lines would be the effect of chlorinated hydrocarbons in causing acneform eruptions. However, the effects of absorption of these chemicals in causing liver damage could only have been brought out in animal experiments.

This brings us to another point stressed by the authors, namely, that usage tests are as important as patch tests in prophesying possible damaging effects to the skin and mucous membranes.

Usage tests under actual conditions of exposure of the chemicals and materials to be used should be the main basis for the evaluation of sensitization potentials of a product and for obtaining an insight into the mild primary irritation which they may cause. Here, the mild primary irritation may not become evident until some time after continuous exposure. Such a usage test should be carried out for at least 30 days.

A combination of the routine "prophetic patch test," as we have described it, plus a usage test for at least 30 days has stood the test of time in my hands. I have carried out this procedure with several hundred cosmetic and pharmaceutical products with proof of its practicability by the reactions encountered in hundreds of thousands of users of these products subsequently.

No matter what testing procedures are devised both in human and in animal experiments, there will always occur unexpected side-effects which cannot be predicted. These occur because we are unacquainted with the unusual physiological and pathological response of the tissues under continuous usage conditions. Such happenstances occurred when unexpected eye damage followed the use of certain shampoos and after the introduction of a formaldehyde-rubber combination as an undercoat for nail polish.

DR. ADOLPH ROSTENBERG JR., Chicago: I am quite interested in this topic because I was for several years the dermatologist with the Food and Drug Administration and, of course, met this problem first hand. Since leaving there and going with Dr. Senear at the University of Illinois, much of my work has been directed along the lines of cutaneous sensitization.

Essentially, the problem is one that is common to practically all branches of science, namely, extrapolation from a limited amount of data. One has, here, two independent variables. There is a biological variable and a statistical variable. It is well to remember that the two are independent.

I am going to talk primarily about sensitization, as I think it is a much more subtle problem than primary irritation. Although I think Dr. Peck is quite correct, that we should not minimize or overlook the primary irritation aspects, this is an easier question to answer. So far as sensitization is concerned, when one works with a human, ordinarily, unless one insists on using the product in the same way that it is proposed to be used, there is different usage and consequently different biological exposure and thereby a different likelihood of developing a sensitization.

For example, if you wanted to test a new hair dye, it would be more or less impossible to use it in the predicting tests as it was going to be used, because, of course, ordinarily hair dyes are used at rather long intervals, and to amass data with the intervals at which the hair dye is ordinarily employed would take an inordinately long period of time; so no matter what you do, you run into difficulties of one nature or another.

Animal tests cannot, of course, be relegated to limbo, nor did either speaker suggest that. The animal has to be used more or less as a screening agent, (*a*) for primary irritation, and (*b*) for strong sensitizers. The guinea pig, with ordinary techniques, will show up only strong sensitizers.

An important point to emphasize, however, and I don't think it has been sufficiently done, is that you should first show that your guinea pig is capable of being sensitized to a known sensitizer. There is not much sense in putting on compound X and saying it does not sensitize,

because you fortuitously may be using a strain of pigs that is just not sensitizable. It should be demonstrated either previously or simultaneously that the pigs in question can be sensitized, say, to 2:4 dinitrochlorobenzene or to poison ivy or to something that is a well-known sensitizer. Then there is some basis for making assertions about the sensitizing proclivities of the unknown.

Finally, a word about statistics. As Dr. Peck emphasized, one usually needs statisticians. I think most of us do not have a sufficient appreciation of that fact. No matter what sort of biological test you employ, that isn't going to affect the mathematics of the statistics; but it is well to recall that the statistical results are no better than the data on which they are based. From the mathematical point of view certain facts are constant regardless of the biology; for example, if you take a group of 200 people and test them and get zero reactors, all you can say is that in the universe at large, there are fewer than 5 chances in 100 that more than 1.5% of the people will react to that material under the conditions of the test employed. That is not too useful a bit of information. All you can say is that not more than 15 people in every 1,000 are going to develop a reaction under those conditions.

Conversely, suppose one somehow had the information that 0.1% of all the people reacted to a given compound, that is 1 in 1,000, which is probably an uneconomical ratio for any manufacturer to operate on, and you grab people at random off the streets in groups of 200, where you know the true incidence is 1 in 1,000, and now you ask the statistician, "How often would you get a reactor in a random group of 200?" Obviously, if it is only 1 in 1,000, you are not going to find a reactor in every group. Actually, in 82% of random groups of 200 you would fail to find a reactor.

All this means is that, actually, to get answers is a very difficult task; that is, to get answers in which one can have real confidence, and it seems to me that much more work has to be done on newer techniques which will enable one to get answers both economically and expeditiously. While I am not suggesting anything better than either Dr. Traub or Dr. Peck has suggested, I feel that a lot of work has to be done in this field.

DR. JOSEPH V. KLAUDER, Philadelphia: As I see it, these newer methods have come into use from this experience of cosmetic manufacturers. It has been observed that the continued daily and prolonged use of a preparation, for example, a deodorant in some persons causes a primary irritant action; I have seen such reactions from deodorants, and have performed patch tests with the deodorant with negative result. I think one rather rarely sees an allergic reaction to a deodorant. Apparently, then, the afore-mentioned reaction is not an allergic one, but an expression of primary irritant action developing after prolonged contact with the skin.

As I see it, Lehman and Draize, in the Food and Drug Administration office, and the cosmetic manufacturers have felt that the conventional methods of cutaneous testing have not gone far enough in eliciting the above-mentioned reaction after continued use of a preparation applied on the skin. As a consequence Draize and Shelanski have for several years employed what they call the "repeated insult method" (A New Technique of Human Patch Tests, *Proc. Sc. Sect., Toilet Goods A.*, No. 19, [May] 1953), in which the studied substance is applied as a patch test every other day for 15 consecutive days, and then there is a rest interval of two weeks. At the end of two weeks the challenge test is applied in order to determine if the substance tested is a sensitizer.

In consulting service to one of these investigators, I studied this "repeated insult method." I was interested to note that at the beginning, say, the first five to eight repeated applications the reaction is clearly negative, and then, with some substances and with some persons it begins to get positive, 1+ or 2+, and remains positive for the remaining latter end of the 15 consecutive tests. Now that has changed somewhat our concept of what is a primary irritant. Such substance is a primary irritant only after repeated applications, in which apparently the skin loses its function to combat a minimum primary irritant action, which was not expressed on the initial applications.

I believe that that is an expression of what has been observed clinically, that a person may react to repeated use of a cosmetic. We see a somewhat comparable state of affairs after prolonged use of soap. Some skins break down and some do not. Burkhardt expressed that as the loss of function of the skin to neutralize alkali. I do not think it is. I observed in my studies (Actual Causes of Certain Occupational Dermatoses, A. M. A. ARCH. DERMAT. & SYPH. **63**:1, 1951), that it is a loss of function of the skin in general. It is, I believe, an expression of the eczematic skin, one with a low threshold of tolerance.

In support of that thesis, on the subjects who reacted toward the end of the repeated patch tests with 1— and 2+, and also on subjects who had no reaction throughout the 15 consecutive applications, I performed patch tests with the 10 fractions of mineral seal oil. I discussed these 10 fractions in a prior communication (Correlation of Boiling Ranges of Some Petroleum Solvents with Irritant Action on Skin, ARCH. DERMAT. & SYPH. **56**:197, 1947). Mineral seal oil was refractioned into 10% fractions. Starting with boiling range of 436 to 534, each fraction had a higher boiling range up to that of spindle oil (588 to 663), which represented the last fraction.

In the afore-mentioned reported study some persons reacted to all the 10 fractions and some reacted only to the first two or three. Of course, there were persons who had intermediate degrees of positive reactions. I regarded the person who reacted to all, or the majority of the 10 fractions, as having a low threshold of cutaneous irritability (or tolerance); whereas reaction to only the first few fractions expressed a high threshold of cutaneous irritability.

So far, a limited number of persons studied who reacted to the end applications of the repeated insult method reacted to all or the majority of the 10 fractions. Conversely, with the same substance other persons who reacted negatively throughout the repeated insult tests, gave positive reactions only to the first few or 5 of the 10 fractions.

DR. MARION B. SULZBERGER, New York: I want to congratulate Dr. Traub, Dr. Tusing, and Dr. Spoor on their courage in venturing into this very complex, very difficult, and very tricky field. I think that what you have heard in the discussion and in their paper illustrates sufficiently well how important and how essential this sort of work really is from the practical standpoint. I hope that they will be able to continue it.

I hope that the previous discussers as well as the presenters have emphasized sufficiently some of the pitfalls here; for instance, Dr. Rostenberg in his discussion brought up the question of extrapolation from a small amount of data to a condition in which there can be almost an infinitely large number of users and an infinite number of applications. The statistics which he mentioned were published by Charles R. Henderson and Edward C. Riley in two articles in the *Journal for Investigative Dermatology;* and then Dr. Rudolf L. Baer and I thought they were so important and valuable that we republished and quoted them in the leading article in the "Year Book of Dermatology and Syphilology for 1944." I think it deserves reemphasis that on finding entirely negative patch tests on 200 random subjects, there is still a 95% likelihood that there might be quite a high incidence of reactions in the general population, i. e., as high as 1.5 per 100 persons.

I would like to emphasize the variability in the conditions of use of different consumer products. One cannot possibly repeat in any form of testing, animal or human, anything like the diverse actual conditions of usage to which these various products are put. To take one of the examples which has already been mentioned, the shampoos; these did not cause any difficulty to the skin or to the scalp. The "reaction" which these particular shampoos elicited was that they produced blindness when got into the eyes. We cannot conceive of skin tests which would have foretold that complication.

The undercoats for the nails were mentioned again. Just contrast, if you will, for a moment, the effects of the undercoats with those of the ordinary nail lacquers. The undercoats were put on the nail to penetrate somewhat into the nail, and this they did. They did it so well that we once had the idea that we should incorporate antifungal agents in these undercoats. We did this, but unfortunately we had no success in treating onychomycosis in this way. The "reaction" which the undercoats produced was a dermatitis of the nail bed and, by the very virtue of the site and the conditions pertaining in that localization, there were very disagreeable affections of very long duration. Because the irritant or allergen (probably allergen) could not get out and remained there, the disease produced in these nails was very often persistent, exceedingly disfiguring, and often painful and incapacitating; as contrasted, for example, with the nail surface lacquers, which remain on the surface and which produce dermatitis, then, not of the nail bed but where they are rubbed into the eyelids or the sides of the neck, or chin, or cheeks—as we all well know. Those two different conditions of use and the resulting differences in the dermatoses produced could not really be foretold by means of any standard form of testing.

I could go on and cite many other such examples. For instance, there are the antifungal agents which were used on the scalps of children and which produced convulsive seizures and deaths in a few of these children. That could not have been foretold by any system of testing.

All this adds up to the fact that nothing will obviate or replace proper tests on large groups under actual conditions of intended use. Nevertheless, despite that fact, one must persist in the direction in which the presenters are now going.

I would like to suggest two additional possibilities for improving the techniques of testing these materials. One of them, I have tried to emphasize repeatedly but apparently have never succeeded in making clear. That is why I would like to repeat here, with all the emphasis I can, that one should establish a ratio between the irritating and/or sensitizing potentials of a known material which is used for a given purpose and those of a new material which is being introduced for the same or a similar purpose. In other words, in that way one at least will be able to tell a manufacturer, "Your product, in the tests to which we have subjected it, has been no worse," or "has been better," or "has been worse," than a standard preparation now in general use for similar purposes.

To illustrate, take a "freckle cream." Freckle creams have been studied very extensively. There was, as a matter of fact, an institute set up several years ago and I was one of the participants in that study, to study the materials contained in freckle creams. It has been established pretty well through millions of users what the incidence of irritation from freckle creams containing 6% ammoniated mercury can be expected to be. Such creams seem to be relatively safe for the purpose for which they are used. There are irritations, there are certainly sensitizations to that material in freckle creams, but they have not been prohibitive either in incidence or in degree. The sale of them is still permitted, and the manufacturers make money from them, and people continue to buy them, so usage has shown that the incidence and kind of damage are not such as to preclude the usefulness of these preparations.

Such a standard "freckle cream" with ammoniated mercury could be contrasted in whatever skin tests one adopts—patch tests, repeated patch tests, repeated insult tests, animal tests—with an unknown bleaching cream, for example, one containing the monobenzyl ether of hydroquinone. One then would establish a ratio between a known product and a new one which is being introduced. The ratio of reactions produced by the known freckle cream with 6% ammoniated mercury to the reactions produced by Benoquin, for example (to give it its trade name) would be valuable information for all of us and to the manufacturers as well.

Another fact which I think should be established is permissible tolerances. Certain agents may be permitted to have a certain number of skin irritations and sensitizations because of their intended conditions of use. Take, for example, therapeutic agents for acne or even for the treatment of psoriasis or the treatment of fungous infections. These certainly might be permitted to have a sensitizing ratio of 1 to 1,000 in an infinite number of users; whereas a cosmetic such as a face powder or hand lotion or eye shadow might not be permitted to have a tolerance of 1 irritation in 100,000 users or even of 1 in 1,000,000 users; I think those are two directions in which we might advance further—(1) by establishing ratios or indices for the relative irritancy and sensitizating potentials of new products compared with an analogous standard product (coefficients of sensitization or irritation); and (2) by agreeing on tolerated or permissible maximal rates of incidence of sensitization or irritation for different categories of consumer products.

Dr. Herbert Rattner, Chicago: This is of great interest to those of us who are members of the Cosmetic Committee of the American Medical Association. The matter of patch tests is always before us because none of the techniques so far devised have proved altogether reliable, and more and more we seem to be depending upon the results reported from usage tests. Because it is necessary to have a base from which to work we have been requiring a minimum of 200 prophetic patch tests, but even this number is likely to be a hardship upon small manufacturers. As you all know, it sometimes requires testing some 300 persons in order to have 200 reportable cases; and such a study can be costly. Even usage data are difficult to evaluate, for manufacturers usually submit as evidence of their products' safety the fact that only occasionally is there a report of injury from the product. There is, of course, no way to estimate the number of unreported cases of injury.

This attempt, therefore, to attain something close to perfection in the way of prophetic patch testing will be watched very closely by the Committee, and it is hoped that the report will stimulate other studies of the subject.

Dr. E. F. Traub, New York: I most sincerely wish to thank the various discussers for their generous comments; realizing that the subject matter which we presented today is so

highly controversial. While we did not hope to be able to settle on any one definite testing method, nevertheless we felt that if the dermatologists did not propose something concrete, the regulatory authorities would come up with some plan which might not be very realistic or practical. Although we realize that our proposal must be subject to appropriate clinical modification in perhaps each instance when special testing is done, it, however, does form a basic pattern which may be extended and it seemed to us that something of this sort was urgently needed. As has been pointed out, it is obviously impossible to do an ideal simulated use test in each instance, but one can interpret clinical results in use test terminology. For example, with a hair dye, I do not believe that the problem would be great even though the process is infrequently used, because once a woman has dyed her hair it must be constantly touched up, and this would constitute the repeated insults which apparently are most desirable for test purposes. As has been pointed out for many preparations, irritation or difficulties do not arise until the product has been on the market for some time, and obviously an experimental use test cannot be carried over a prolonged period of months or years. Here, perhaps, the animal tests which can use higher dermal insult concentrations might indicate that there will be trouble later on.

The objection to doing repeat patch tests on the same subject, carrying out such a procedure for perhaps 10 or 15 repeats is its practical impossibility, primarily because of the difficulty in obtaining subjects who would submit to the course. Even if we were able to do these patch tests on subjects, they would not always give the best results because they cannot simulate the conditions of actual use. Furthermore, patch tests of the closed type often give a mild positive reaction in a relatively high percentage of cases and thus create the false impression that the preparation if used as indicated would cause trouble. This is because volatile substances that may be in a given preparation would evaporate under normal use conditions but when sealed in would irritate.

It has been our experience that continued or repeated patch tests can elicit and develop positives which would never show up under use conditions; as well as the reverse status, of not revealing potential trouble makers.

Again we wish to stress that we merely propose a basic formula to be modified as needed in a given case. We felt that even a rough formula such as ours was better than not having any such working plan.

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TREATMENT OF RHUS DERMATITIS WITH TOPICAL HYDROCORTISONE

A Clinical Evaluation

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THE FAILURE of older remedies—boric acid or permanganate soaks; topical antihistamines; calamine lotion; and superficial anesthetic agents—to prevent spread and to alleviate symptoms of Rhus dermatitis has led to the recent study of corticotropin (adrenocorticotropic hormone) and cortisone in this condition. At the present time a divided opinion exists as to the value of these agents in this disease. Such a variance in reported results can be appreciated by a consideration of the nature of Rhus dermatitis, especially the protean course of the disease in different individuals.

In the treatment of 15 patients with Rhus dermatitis by the use of 500 to 1000 mg. of oral cortisone over a four- to seven-day period, Wrong and Smith noted a good to excellent response in 73% of their cases. Falk reported a series of nine patients hospitalized because of Rhus dermatitis. These patients were treated for three days with either oral cortisone or intramuscular corticotropin. Falk reported relief of pruritis and improvement in swelling within 12 to 36 hours in 88%. The average hospital stay was reduced to 3.3 days, as compared with a hospitalization period of 6.6 days in a prior random control group. It was noted, however, that upon completion of the three-day therapy regime, most of the patients had a return of pruritis. A single case of Rhus dermatitis which showed a rapid response to intramuscular corticotropin has been reported by Rosenberg and his associates. Bergstrom reported a case of severe angioneurotic edema secondary to Rhus dermatitis which was treated with 50 mg. of cortisone every eight hours. Improvement was noted within 12 hours, and complete subsidence occurred after 48 hours of cortisone therapy.

Ekblad's series of nine patients with severe Rhus dermatitis demonstrated no objective improvement in the lesions or shortening of the course of the disease by the use of oral cortisone or parenteral corticotropin over a one-to-two-day period. Only 50 to 75% abatement of subjective symptoms was noted in any of his patients.

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For this study 0.2% hydrocortisone lotion was furnished by Smith, Kline & French Laboratories, Philadelphia; 1.0 and 2.5% hydrocortisone ointment by Merck & Company, Inc., Rahway, N. J., and 2.5% hydrocortisone cream by The Upjohn Company, Kalamazoo, Mich.

Hoagland treated 16 cases of Rhus dermatitis with 700 mg. of oral cortisone over a four-day period. He noted no greater incidence of healing than was obtained on a placebo series. He likewise noted no beneficial effect after topical treatment of several patients with a 2.5% cortisone acetate ointment.

With the differences in opinion expressed by the above authors concerning the value of corticosteroids in Rhus dermatitis, a further trial was felt to be indicated. Topical hydrocortisone was employed, so as to facilitate ambulatory treatment. This report presents an evaluation of 79 patients who developed Rhus dermatitis. The six topical preparations used were: 0.2% hydrocortisone lotion; 1.0% hydrocortisone ointment; 2.5% hydrocortisone ointment; and 2.5% hydrocortisone cream. In addition, placebos in the form of lotion and ointment were employed. Seventy-seven courses of topical hydrocortisone therapy were given, and 15 patients received placebos.

Our study revealed no beneficial effect by the hydrocortisone preparations on the spread or symptomatology of ivy poisoning, save in four cases which presented massive angioneurotic edema as the original symptom. The case histories of two of the latter are briefly described, and are seen to closely resemble the case reported by Bergstrom.

METHODS

At the time that a diagnosis of Rhus dermatitis was made, a follow-up card was prepared and the patient was sent to the hospital pharmacy. The diagnosis was then recorded by the hospital pharmacist, who distributed one of the six agents to the patient in an unlabeled tube. The pharmacist alone possessed information regarding the therapeutic agent or placebo employed in each case. The patients were instructed to apply the agent twice daily to the affected areas, and were then seen daily for evaluation. The topical substances employed in each case were not known by those evaluating the patient. In some cases, if no beneficial effect was noted on the original treatment, another topical agent was distributed in the same manner by the pharmacist. The only exceptions to the above nonselective program occurred in four patients who were immediately admitted to the hospital at the time of diagnosis because of severe angioneurotic edema. These patients were immediately treated with either 1.0% or 2.5% hydrocortisone ointment. These cases are not included in the statistical data, as no similar cases were available for any other treatment or placebo regimen.

The cases studied were graded as to severity at the time therapy was commenced. The lesions were considered as 1 + in severity if the patient complained of mild pruritis and showed faint erythema. With intense itching, marked erythema and vesicle formation, the severity was graded 2 +. The addition of weeping and excoriation led to a 3 + designation. Those patients who presented themselves with massive swelling of the face, the arms, or genitals, and with intense pruritis, without vesicular lesions or weeping were considered 4 + in severity. This grading is admittedly arbitrary.

The results of therapy were similarly graded with the designations of "No improvement," "Mild improvement," "Moderate improvement," and "Marked improvement." In the grouping "No improvement" were placed all cases which showed either (*a*) increasing symptoms after two days of therapy; (*b*) direct or distant spread of lesions after two days of therapy, or (*c*) continuing symptoms, after 10 days of treatment. Mild, moderate, and marked improvements could not be so exactingly defined, but reflected an indication of the reduction of subjective symptoms and objective signs over the treatment period.

RESULTS

The response to the use of topical hydrocortisone therapy in 77 courses, and topical placebo management in 15 courses is tabulated in the Table. It is noted that 60% of those cases receiving placebo therapy showed no improvement, while

13.3% and 26.7% of the same group showed mild and moderate improvement respectively. In those patients receiving the various topical hydrocortisone preparations, from 61 to 83% showed no improvement, while the remainder showed mild or moderate improvement. An attempt was made to correlate the response to the various topical hydrocortisone therapies with the degree of severity of the lesions at the time therapy was started. Correlation was also attempted to determine any relationship between the duration of the process before treatment and the response to hydrocortisone therapy. Neither correlation could be considered of value from a therapeutic viewpoint, as many cases which were of the mildest nature at the time of original hydrocortisone therapy showed no greater evidences of improvement than did those cases which were most severe at the time hydrocortisone was started. Furthermore, hydrocortisone treatment within 24 hours of the onset of symptoms seemed to offer no greater percentage of beneficial effects than was obtained if treatment was delayed 48 to 72 hours.

It is thus obvious that in our routine series no beneficial effect could be ascribed to topical hydrocortisone lotion, ointment or cream. Four severe cases were seen, however, which, because of their marked angioneurotic edema at the time

Response to Various Treatments in Ninety-Two Instances of Rhus Dermatitis

	Percentage				
	Placebo	0.2% HC* Lotion	1.0% HC* Ointment	2.5% HC* Ointment	2.5% HC* Cream
No improvement	60.0	83.3	65.0	61.1	76.5
Mild improvement	13.3	5.6	10.0	11.1	5.9
Moderate improvement	26.7	11.1	25.0	27.8	17.6

* HC, hydrocortisone.

of onset, were hospitalized and given 1.0% or 2.5% hydrocortisone ointment topically. These four all showed an immediate and excellent response to hydrocortisone ointment.

REPORT OF CASES

1. A 22-year-old man gave a past history of severe Rhus dermatitis 10 years previously, which required three weeks for facial edema to clear. He was admitted to this hospital 48 hours after exposure to Rhus plants, and 24 hours after the onset of swelling of eyelids, cheeks, and forehead. At the time of admission the swelling was of such severity that he could not open either eye. He complained of severe pruritis and showed slight erythema of the affected facial areas. Immediately upon admission 2.5% hydrocortisone ointment was applied topically to all areas of swelling. Within six hours the swelling was reduced so that it was possible to examine his pupils. At that same time the pruritis had cleared, and the erythema had lessened. After four applications over a 48-hour period, he showed complete clearing of all allergic reactions, and was discharged from the hospital.

2. A 22-year-old man was engaged in fighting a forest fire in an area known to contain large growths of Rhus plants. Within 24 hours he noted extreme pruritis of face, eyes, and genitalia. At the time of admission to the hospital, 60 hours after exposure, moderate swelling of the left cheek and extreme swelling of the foreskin and shaft of the penis were present. Extreme pruritis was present, and moderate erythema was noted. No vesicular formation was present. Upon admission 2.5% hydrocortisone ointment was applied to the involved areas. The ointment was used every 12 hours. At the end of 24 hours of treatment there was no pruritis, only slight redness, and a marked reduction in facial and genital swelling. After 48 hours of treatment the patient exhibited no abnormalities and was discharged from the hospital.

COMMENT

The use of topical hydrocortisone in cases of Rhus dermatitis manifesting the routine syndrome of pruritis, redness, and vesicle formation, was found to be valueless. There was no greater lessening of the subjective symptoms or objective signs than was obtained by the use of placebo management. The same direct extension or distant spread noted in the placebo-treated cases occurred to the same extent in those cases receiving topical hydrocortisone therapy.

Of interest were those cases which showed a massive hypersensitivity reaction as the sole manifestation of ivy contact. All of these showed massive swelling of regions of the body, with marked pruritis, slight redness, and absence of vesicular eruptions. There were four such cases in our group, all of which showed immediate and dramatic effectiveness of topical hydrocortisone therapy. The extreme severity of these patient's lesions precluded control studies with the use of placebo therapy. However, the results obtained following topical hydrocortisone therapy in this limited group were most striking and encouraging clinically.

SUMMARY

Seventy-nine patients with Rhus dermatitis of varying degrees of severity were treated with topical hydrocortisone or a similar appearing topical placebo.

A total of 92 courses of therapy were evaluated in these patients.

In the usual case, as characterized by redness, pruritis, and vesicular eruption, topical hydrocortisone therapy had no greater beneficial effect on the signs, symptoms, or spread than did placebo therapy. Thus in this, the usual type of Rhus dermatitis, therapy with topical hydrocortisone cannot be recommended as curative or alleviating.

Four cases of Rhus dermatitis manifested by the presence of massive regional swelling with extreme pruritis, and the absence of vesicular eruption, were treated with topical hydrocortisone with excellent response. This severe form of ivy poisoning with its extreme allergic picture, does offer a limited use for topical hydrocortisone therapy in Rhus dermatitis.

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ROLE OF ANTIBIOTICS IN THERAPY OF ACNE

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THE ROLE of pyogenic bacteria in the production of acne pustules has evoked considerable discussion among dermatologists, and there is a wide divergence of opinion concerning its importance. Comparative studies reveal that most authors agree that the management of the recurrent cystic and large indurated acne lesions presents a therapeutic challenge. In Becker's series of 65 patients he performed bacteriologic studies and recovered hemolytic Staphylococcus albus in 7, nonhemolytic Staphylococcus albus in 25, hemolytic Staphylococcus aureus in 3, nonhemolytic Staphylococcus aureus in 12, a mixed growth of bacteria in 8, and no growth in the remaining 10. Sensitivity tests indicated that the organisms were more highly sensitive to penicillin than to the other antibiotics; however, clinical tests did not support these findings.

Sulzberger and Baer reported excellent results with local injections of aqueous solutions of penicillin and of bacitracin directly into the cystic lesions after aspiration of the purulent contents. Andrews and his associates reported that penicillin was of least value in the treatment of acne but that chlortetracycline (Aureomycin) and oxytetracycline (Terramycin) gave good results.

They were enthusiastic about the success of their studies and suggested that antibiotic therapy was an integral part of the modern approach to the treatment of acne. Becker found the orally administered antibiotics to be of value in the treatment of acne pustules, but he also noted that when the drug was discontinued the condition recurred. He was able to obtain a satisfactory result in many of his patients by the continued administration of small periodic maintenance doses of the selected medicament. In his discussion of Becker's report, Sulzberger suggested that the beneficial effect of the antibiotics in acne might be due to their action against internal foci of infection rather than a direct effect on the cutaneous lesions.

My confreres and I, at the University of Maryland Hospital, have been conducting a series of surveys on the effect of the various antibiotics in the treatment of dermatoses. In the course of these studies we have administered these drugs orally and locally to 391 patients with acneform eruptions. The patients were classified into three groups: (1) acne vulgaris; (2) acne conglobata, and (3) acne rosacea. During the time these patients received antibiotic therapy, no other means of treatment was used. Penicillin, chlortetracycline, chloramphenicol (Chloromycetin), oxytetracycline, erythromycin, and carbomycin (Magnamycin) were administered systemically to one series of patients and by local application to another.

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This study was supported by grants-in aid from the Abbott Laboratories, Charles Pfizer & Company, and the Upjohn Company.

Read in the Section on Pharmaceutical Therapeutics of the American Academy of Dermatology and Syphilology at the 12th Annual Meeting, Chicago, Dec. 10, 1953.

LOCAL THERAPY

The various antibiotic ointments were used in the local treatment of 72 patients with acne (Table 1). A statistical survey indicated that such therapy of acne vulgaris with the antibiotics produced temporary improvement in only a very small percentage of the patients. The possibility of producing acquired contact sensitivity to these drugs by long continued local application is a major contraindication to such therapy, particularly in view of the fact that the results of such treatment of acne are generally unsatisfactory.

SYSTEMIC THERAPY

A series of 18 patients was treated with intramuscular injections of procaine penicillin in oil. Each patient received 300,000 units daily for 10 days, after which a maintenance dose of 300,000 units a week was administered for four weeks. Improvement was not noted in any of this group and because the results were generally unsatisfactory this method of treatment was discontinued.

TABLE 1.—*Local Antibiotic Therapy of Acne*

Drugs	No. Cases	Satisfactory Result	Temporary Improvement	Unimproved	Percentage Improved
Penicillin ointment	15	0	3	12	20%
Chlortetracycline ointment	12	0	4	8	33%
Oxytetracycline ointment	15	0	4	11	26%
Chloramphenicol ointment	18	0	6	12	33%
Erythromycin ointment	8	0	2	6	25%
Carbomycin ointment	4	0	0	4	0

Forty-three patients were treated with chlortetracycline. An initial dose of 1 to 2 gm. was followed by 0.5 gm. four times daily. After three weeks the dose was reduced to 250 mg. two or three times daily, depending on whether or not the patient developed any gastrointestinal reaction. Complete involution of the lesions was noted in three patients with acne vulgaris and three with acne conglobata. There was partial improvement in one patient with acne conglobata and temporary improvement in a large percentage of all three types of acne. Many patients retained a satisfactory result as long as the medication was continued, but as soon as antibiotic therapy was stopped the lesions recurred.

Oxytetracycline was administered to 93 patients with acneform eruptions (Table 2). Six patients with acne vulgaris and five with acne conglobata noted complete involution of the lesions. There was partial improvement in eight patients with acne vulgaris and two with acne conglobata. Sixty patients obtained temporary improvement while on oxytetracycline therapy, but when the drug was discontinued the lesions recurred. In 20 of these patients it was possible to retain a satisfactory result with a maintenance dose of 250 mg. daily; however, there was recurrence of lesions within one to two weeks after therapy was discontinued. The initial dosage was the same as used for chlortetracycline.

Chloramphenicol was administered to 68 patients with the various forms of acne, with the same dosage schedule used for those individuals treated with chlortetracycline and oxytetracycline. Two patients with acne vulgaris and three with acne

conglobata obtained excellent results. Fifty-six patients showed temporary improvement while administration of the drug was continued, but relapses were noted as soon as the dosage was stopped. One medical student maintained satisfactory result with a dosage of 250 mg. every other day.

TABLE 2.—*Statistical Study of Systemic Antibiotic Therapy of Acne*

Antibiotic	Diagnosis	No. Cases	Complete Involution of Lesions	Temporary Improvement	Partial Improvement	Unimproved	Lost from Observation
Oxytetracycline	Acne vulgaris	45	6	26	8	4	1
	Acne rosacea	9	..	6	..	2	1
	Acne conglobata	39	5	28	2	3	1
Chlortetracycline	Acne vulgaris	22	3	18	..	..	1
	Acne rosacea	5	..	2	..	3	..
	Acne conglobata	16	3	10	1	2	..
Chloramphenicol	Acne vulgaris	39	2	37	..	..	..
	Acne rosacea	3	..	3	..	..	..
	Acne conglobata	26	3	16	4	3	2
Erythromycin	Acne vulgaris	42	2	39	1	..	..
	Acne rosacea	4	..	2	..	1	1
	Acne conglobata	29	1	23	2	3	..
Carbomycin	Acne vulgaris	11	0	5	..	6	..
	Acne rosacea	2	..	0	..	2	..
	Acne conglobata	9	0	2	1	6	..

TABLE 3.—*Systemic Antibiotic Therapy of Acne*

Antibiotic	No. Cases	Route	Initial Dosage	Maintenance Dose	Efficiency	Choice
Penicillin	18	Intramuscular	300,000 units daily	300,000 units weekly	Inefficient	...
Chlortetracycline	43	Oral	1-2 gm. daily	250 mg. 2-3 times daily	++++	1st
Oxytetracycline	93	Oral	1-2 gm. daily	250 mg. 2-3 times daily	++++	1st
Erythromycin	75	Oral	0.2 gm. daily	0.1 gm. twice daily	++++	1st
Chloramphenicol	68	Oral	1-2 gm. daily	250 mg. 2-3 times daily	++++	3d
Carbomycin	22	Oral	0.2 gm. daily	0.1 gm. twice daily	++	2d

Seventy-five patients were treated with erythromycin. The initial dosage was 200 mg. every six hours. After three weeks the dosage was reduced to 100 mg. every six hours. Two patients with acne vulgaris and one with acne conglobata obtained a satisfactory result. Partial improvement was noted in 3 patients, and 69 noted temporary improvement while the administration of the drug was continued.

A small series of 22 patients has been treated with carbomycin, and many of these patients are still under observation. This drug, thus far, has not been as effective as the other broad spectrum antibiotics. The dosage schedule was the same as used for erythromycin.

COMMENT

Penicillin by injection proved to be of little value in the treatment of acneform eruptions, but the broad spectrum antibiotics have a definite place in a therapy of acne vulgaris and acne conglobata. In view of the fact that long-continued administration of these drugs is necessary to obtain and maintain a satisfactory result, extreme caution must be observed to avoid serious adverse reactions.

A careful history and a complete physical survey should be a part of the treatment routine, and repeated blood pictures are necessary. Continuous administration of any of these drugs without rest periods is not advisable. In order to avoid the destruction of the normal flora of the body, rest periods of two weeks alternating with two weeks of antibiotic therapy have proved to be the most satisfactory method.

The broad-spectrum antibiotics do not replace any of the standard methods of treatment in present day use but are intended as supplementary therapy.

Statistical studies indicate that from the standpoint of satisfactory results and the lack of serious adverse reactions, oxytetracycline and chlortetracycline are antibiotic drugs of first choice. The most serious drawback of both of these is the high percentage of gastrointestinal reactions. Erythromycin is also of great value, and in the series tested the adverse reactions have been minimal.

SUMMARY AND CONCLUSIONS

The broad spectrum antibiotics are of value as supplementary therapy in the management of acne vulgaris and acne conglobata, and do not replace x-ray, dietary measures, and proper local treatment.

The local use of antibiotic therapy in the treatment of acne is not recommended, because of the small number of satisfactory results and the danger that long continued local aplication of these drugs may produce acquired contact sensitivity.

In this series, penicillin by injection was of no value in the treatment of acne.

Oxytetracycline, chlortetracycline, and erythromycin are the drugs of first choice.

Chloramphenicol is as effective as oxytetracycline, chlortetracycline, and erythromycin in the treatment of acne, but its use is not recommended because of the possible production of blood dyscrasias.

Long-continued administration of the antibiotics without rest periods is not advisable.

Improvement may be maintained in a high percentage of cases by administration of subtherapeutic maintenance doses.

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USE OF SYNTHETIC ESTROGENIC SUBSTANCE CHLOROTRIANISENE (TACE) IN TREATMENT OF ACNE

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CINCINNATI

IN AUGUST, 1952, an editorial in *The Journal of the American Medical Association* was devoted to a new long-acting estrogen, TACE. Because of its importance, major portions of the editorial are quoted herewith.

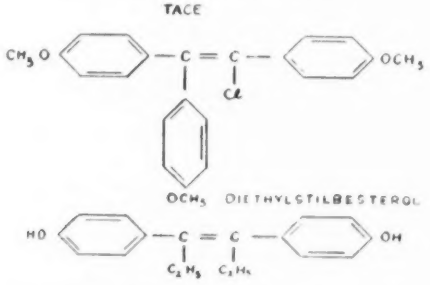
The discovery that the synthetic compound diethylstilbestrol possessed high estrogenic activity when administered orally prompted a search for related compounds with a more prolonged activity. In 1942, Robson and his associates reported that the triphenyl ethylene derivative diethoxy-triphenyl bromoethylene (αα-di[-*p*-ethoxyphenyl] β-phenyl bromoethylene), or D. B. E., showed a markedly prolonged estrogenic action in mice subjected to ovariectomy when given in doses somewhat greater than those producing a threshold response. The English investigators showed this prolonged effect was due to the fact that, on introduction into the body, D. B. E. in contrast to the estrogenic substances then available was not immediately destroyed or excreted in the urine but was stored in a number of tissues, particularly the fat, and was only gradually eliminated from the body. It was further shown that this compound was a proestrogen, a term introduced by Emmens to describe compounds that do not act directly on the vagina but must be absorbed into the body and metabolized to a true estrogen before inducing their effects.

In this country, in 1940, Shelton and his co-workers first synthesized a series of triphenyl chloroethylene derivatives, which were pharmacologically investigated by Thompson and Werner, with particular reference to chlorotrianisene (TACE, The Wm. S. Merrell Company).§

They have shown that this compound, like D. B. E., is initially stored in body fat and is slowly liberated and metabolized, probably largely in the liver, to a much more potent estrogen than the parent substance. In addition they noted certain differences between the effect elicited by TACE and by the estrogen hexestrol when given to mice in doses of equal biologic potency, as judged by uterine and vaginal changes. Thus TACE, unlike hexestrol, did not cause enlargement of the pituitary gland. Furthermore, TACE caused only a slight increase, while hexestrol caused a marked increase, in the weight of the adrenals, and TACE resulted in less ovarian atrophy than hexestrol.

Fat storage, resulting in prolonged activity, occurred following oral administration of large doses of chlorotrianisene.

TACE (chlorotris [*p*-methoxyphenyl] ethylene, tri-*p*-anisylchloroethylene, $C_{23}H_{21}ClO_3$) is represented by the structural formula:



TACE is the trademark of the Wm. S. Merrell Company, Cincinnati, for its brand of chlorotrianisene (tri-*p*-anisylchloroethylene).

§ References 5 to 7.

Chlorotrianisene shares the actions and uses of the estrogens. It possesses, however, certain peculiar attributes not common to other estrogens:

When administered orally, the amount of estrogenic active substance recovered in the stool exceeds the amount originally administered in the form of chlorotrianisene. This indicates that by some metabolic process the potency of the drug is enhanced. A hint of the probable locale of this enhancement is furnished by experiments in which the activity of chlorotrianisene is increased by incubation with liver homogenates.

In the dosages used in experimental studies on laboratory animals, chlorotrianisene induced less pituitary or adrenal hyperplasia than other estrogens.

The compound is stored in the body fat, from which it is slowly released over a period of time, varying with the amount administered. Therefore, its action will persist for varying periods following discontinuance of the drug.

Chlorotrianisene has a lower milligram equivalent than other synthetic estrogens, and doses are higher for comparable effects (capsules TACE [chlorotrianisene] 12 mg. in corn oil, U. S. patent 2,430,891).

RATIONALIZATION FOR USE OF ESTROGENIC SUBSTANCES IN TREATMENT OF ACNE

Acne, a chronic inflammatory disease of the skin involving chiefly the pilosebaceous structures, has been termed physiologic and pathologic during adolescence.

Bacteriological approach to the etiology of acne has been controversial.

Investigators emphasize that a number of factors rather than a single factor lead to the various manifestations of acne. Predisposing conditions include the following:

1. gastrointestinal disturbances
2. dietary indiscretions and allergic reactions
3. nutritional deficiencies
4. psychogenic factors
5. focal infections
6. disturbances of metabolism
7. endocrine dysfunction

I am of that group of investigators who believe that an endocrine imbalance is a partly causative factor of acne. This imbalance is not necessarily due to an excessive production of any one hormone, but, rather, is the result of a variation in the normal production ratio of one hormone to another or a disturbed balance between the two hormones resulting in insufficient estrogenic potency to protect against the acnegenic effect of androgens.

From 1950 to 1953 various investigators have reported on oral estrogenic therapy in the treatment of acne.

Estrogenic therapy appears to be logical and warranted where general health is good and where there is history of marked and regular flares of eruptive phenomena associated with the menstrual cycle in females, where acne is (or proves to be) recalcitrant, or where response to other measures is too slow, in males and females, and where severe involvements with acne cystica, acne indurativa, and acne conglobata will produce permanent scarring before other therapy can control.

Estrogenic therapy must be administered judiciously, with adjustment of the dosage to meet the patient's changing requirements, with frequent and regularly maintained observation and recheck of the patient, and with individualization of the prescribed dosage. Essentially, estrogens inhibit the gonad-stimulating function of the anterior lobe of the pituitary gland. If given to females immediately after menstruation, in too large doses, they may inhibit ovulation. If given promiscuously, they may stimulate in females ovarian cyst formation and uterine hyperemia and cause in susceptible males proliferation of mammary ductule tissue and gynecomastia.

METHOD OF ADMINISTRATION OF ESTROGENIC SUBSTANCES USED IN THIS STUDY

Synthetic Estrogenic Substance (Chlorotrianisene).—Females: When estrogenic therapy appeared logical and warranted, a test course of one capsule every other day was given during the last half of one ovulatory cycle (total, seven capsules). Patients were observed weekly. Development of moderate dysmenorrhea or delay of menses for one week or longer was interpreted as indication to reduce the dosage.

If the test course produced no significant dysmenorrhea or delay in the menstrual cycle, it was repeated the following month. If the test course produced some lessening of premenstrual or menstrual flare, the dosage was maintained for several more cycles. After three such cycles, without flare of acneform eruption, the dosage was gradually diminished and the administration finally stopped.

If the test course produced moderate dysmenorrhea or delay of menses for one week or longer, the dosage was reduced to one capsule every other day the last week of the cycle (total, four capsules).

If the test course produced no lessening of premenstrual or menstrual flare after two cycles, the dosage was increased to 1 capsule every other day the third week and 1 capsule daily the fourth week (total, 10 capsules). If the increased schedule proved inadequate, the dosage was increased to 1 capsule daily (total, 14 capsules, or alternating 1 capsule one day and 2 capsules the next (total, 21 capsules), or 2 capsules daily (total, 28 capsules).

The test course during two to three cycles was used to determine whether dosage should be increased or reduced in order to attain maximum tolerance dose.

To patients at the menopause (natural or artificial) one capsule daily was given.

Males: When estrogenic therapy appeared logical and warranted, a course of medication consisting of one capsule every other day was given to patients over 20 years of age.

To males with severe cystic and conglobata involvements, the following dosage schedules were prescribed, depending upon requirements: one capsule for two days, nothing the third day, one capsule for the following two days, and so on, or one capsule daily for three weeks, followed by one week of rest, and repetition of therapy course, or one capsule daily.

One capsule every third day was prescribed for patients under 20. Many males 18 or 19 years of age tolerated the same schedule as was used for those over 20.

Weekly rechecks were maintained on males (as on females).

Comment.—In the group of 151 patients with various types of acne treated with the synthetic estrogenic substance chlorotrianisene (Table 1), the average duration of therapy was 3.79 months.

TABLE 1.—*Results of Treatment in 151 Cases of Various Types of Acne with the Synthetic Estrogenic Substance Chlorotrianisene (TACE)*

	Age	Cases	Duration of Therapy, Mo.	Cleared	Controlled	No Improvement	Dysmenorrhea	Cycle Upset	Thyroid Extract	Previous X-Rays	Current X-Rays	Previous Hormones	Antibiotics	Gonadotrophic Hormone	Bacterial Antigen
119 Females															
Acne vulgaris	−20	20	4.5	6	14	..	1	3	14	10	3	11	..	15	8
48	+20	22	4.1	12	10	..	2	1	6	17	2	3	1	16	12
	+30	6	4.2	1	5	..	..	1	2	2	1	..	..	4	1
Acne cystica and indurativa.	−20	16	4.5	10	6	..	..	7	6	8	5	7	1	15	14
65	+20	31	4.8	15	16	..	2	4	15	22	7	22	7	26	24
	+30	18	4.1	11	7	..	3	3	10	16	3	11	4	9	12
Acne rosacea	+30	6	2.3	1	5	..	1	..	3	3	1	2	..	1	2
6															
32 Males															
							Gynecomastia								
Acne vulgaris	−20	7	3.8	2	5	..	1	..	..	5	3	4	1	6	3
8	+20	1	4.0	1	..	..	..	..	..	..	..	1	..	..	..
Acne cystica, indurativa, and conglobata	−20	16	3.5	2	14	..	1	..	..	8	6	7	4	15	14
	+20	7	3.7	2	4	1	..	..	2	4	2	3	3	6	5
24	+30	1	2.0	..	1	..	..	..	..	..	..	..	1	..	1

Fifty-eight patients had low basal metabolic rates and were placed on thyroid extract in appropriate dosages. Twenty-two patients received antibiotics to control pustular exacerbations.

Response to chlorotrianisene appeared to be in no way influenced by previous therapeutic agents—roentgen radiation, local chemical, bacterial antigen, or gonadotropic substance. Seventy-one patients had had previous estrogenic therapy of some type (in many instances poorly administered).

Ninety-five patients had had previous x-ray therapy. Thirty-three others, who had severe indurated cystic acneform eruptions, were given x-rays concurrently with chlorotrianisene.

Mild dysmenorrhea was experienced by nine females. Some mild disturbance of the menstrual cycle (not necessitating changes in dosage schedules) was reported by 58 females. In 19 patients moderately severe disturbances of the cycle occurred. All symptoms were controlled by manipulation of dosage.

Gynecomastia occurred in only two males, one aged 15 and one aged 17 years, both on a dosage schedule of one capsule every other day. The patient, aged 15, experienced symptoms after he had been on chlorotrianisene for four months. Symptoms persisted for two months, and chlorotrianisene was not resumed because the acne had progressed satisfactorily beyond the point of requiring estrogenic therapy. The other patient, aged 17, experienced mild gynecomastia after therapy with chlorotrianisene for four and one-half months. Symptoms persisted for just a few weeks, and the patient was able to resume chlorotrianisene, one capsule every four days, without recurrence of symptoms.

No feminizing symptoms appeared in any male patient, and no male over 20 experienced any lowering of libido.

In the entire group, 63 patients (41.7%) cleared completely; 87 patients (57.7%) were controlled satisfactorily, and 1 patient failed to show any response.

Conjugated Estrogenic Substance (Premarin).—Females: When estrogenic therapy appeared logical and warranted, initial dosage of 0.625 mg. daily was prescribed for the last half of the ovulatory cycle. Dosage was increased to 1.25, to 3.0, or to 6.0 mg. daily, as necessary. Moderate dysmenorrhea or delay of menses for more than one week was considered indication to reduce dosage (which was kept, always, at maximum tolerance level).

After two to three cycles without amelioration of the acneform flare and in the absence of significant dysmenorrhea or delay of menstruation by more than one week, the dosage was increased from the starting level of 0.625 mg. to 1.25 mg., for the next two to three cycles. The dosage was further increased, as required, staying within the above standards of tolerance.

For patients at menopause (natural or artificial) the dosage was usually 1.25 mg. daily.

Males: When estrogenic therapy appeared logical and warranted, dosages of 0.625 mg., and in some cases, 1.25 mg. daily, were prescribed for patients under 20. For patients over 20, the usual dosage was 1.25 to 3.0 mg. daily.

Weekly rechecks were maintained on males (as on females).

Comment.—In the group of 154 patients with various types of acne treated with the conjugated estrogenic substance (Table 2) the average duration of therapy was 8.4 months.

TABLE 2.—*Results of Treatment in 154 Cases of Various Types of Acne with the Conjugated Estrogenic Substance (Premarin)*

							115 Females								
	Age	Cases	Duration of Therapy, Mo.	Cleared	Controlled	No Improvement	Dysmenorrhea	Cycle Upset	Thyroid Extract	Previous X-Rays	Current X-Rays	Previous Hormones	Antibiotics	Gonadotropic Hormone	Bacterial Antigen
Acne vulgaris	−20	26	7.8	1	17	8	2	8	6	12	9	..	..	12	9
53	+20	22	8.5	4	12	6	2	7	5	6	10	1	..	10	6
	+30	5	9.4	1	3	1	1	..	1	2	1	1	1	1	2
Acne cystica and indurativa	−20	14	9.7	3	7	4	1	6	4	7	6	..	..	13	9
59	+20	30	10.6	5	14	11	4	7	7	17	14	2	4	27	27
	+30	15	9.6	2	6	7	5	5	6	9	5	1	1	7	9
Acne rosacea	+30	3	8.6	..	2	1	1	1	..	3	..	..	..	..	..
3															
							39 Males								
							Gynecomastia								
Acne vulgaris	−20	11	6.3	..	6	5	1	..	..	3	8	..	..	7	7
15	+20	3	10.3	..	2	1	..	..	..	2	1	..	..	2	1
	+30	1	13.0	..	1	..	..	..	..	..	1	..	..	1	..
Acne cystica, indurativa and conglobata	−20	17	8.1	2	8	7	1	..	..	7	7	..	5	14	13
	+20	5	4.6	..	3	2	..	..	..	4	1	..	..	5	5
23	+30	1	8.0	..	1	..	..	..	..	1	..	..	..	..	..
Acne rosacea	+30	1	4.0	..	..	1	..	..	..	..	..	..	..	..	..
1															

Twenty-nine patients had low basal metabolic rates and were placed on thyroid extract, in appropriate dosages. Eleven patients received antibiotics to control pustular exacerbations.

Response to the conjugated estrogenic substances appeared to be in no way influenced by previous therapeutic agents—roentgen radiation; local chemical, bacterial antigen, or gonadotropic substance. Five patients had had previous estrogenic therapy of some type.

Seventy-three patients had had previous x-ray therapy. Sixty-three others, who had severe indurated cystic acneform eruptions, were given x-rays concurrently with the conjugated estrogenic substance.

Mild dysmenorrhea was experienced by 16 females. Some disturbance of the menstrual cycle was reported by 34 females. All symptoms were controlled by manipulation of dosage.

Forty-seven females who did not show adequate response after several months on conjugated estrogenic substance were placed on chlorotrianisene. Forty-two of these patients improved after such change in estrogenic therapy. Ten males who did not show adequate response on conjugated estrogenic substance all showed prompt improvement on chlorotrianisene.

Gynecomastia occurred twice in 39 males. Symptoms subsided promptly on discontinuance of medication.

Of the entire group, the acne cleared completely in 18 patients (11.68%), was controlled in 83 patients (53.8%), and failed to respond in 53 patients (34.4%).

SUMMARY

Chlorotrianisene (TACE) is described.

References are cited to bacteriological studies and the various predisposing conditions which lead to manifestations of acne.

References are cited for rationalization of use of estrogenic substances and results obtained from use of oral estrogenic therapy in the treatment of acne.

Results obtained with the synthetic estrogenic substance chlorotrianisene (TACE) are compared with results obtained with the conjugated estrogenic substance (Premarin).

CONCLUSIONS

Inasmuch as acne is an eruptive phenomenon attributable to a number of causes and influencing factors, rather than to a single factor, treatment must be selective and individually administered. Such treatment must combine topical, internal, and roentgen-irradiation measures, adapted to the patient's requirements.

Thorough cleansing with salicylic-acid-containing soap and local application of an antibacterial lotion combining sulfur, derivatives of resorcinol (Resorcin), and mercury (sometimes preceded by use of a solvent to remove excess oily secretion) are of great importance, as is concomitant local therapy for control of seborrhea involving the scalp.

Any pathological condition (including focal infections) should be corrected, according to the principles of general medicine. Dietary restrictions should at least limit a high carbohydrate and fat intake. Such restrictions should forbid chocolate, sea foods, and the fat fraction of milk. Essentially, a diet of meat and green or colored vegetables in unlimited amounts seems reasonable.

Thyroid extract is beneficial to patients having a low basal metabolic rate.

Vitamin A should be administered where there is clinical evidence of insufficiency.

Patients with inflammatory infiltrations, superficial or deep, and with indurated cystic lesions benefit from administration of antibiotics, bacterial antigens, particularly Staphylococcus ambotoxoid (E. R. Squibb & Sons), and vaccines. Antibiotics may have to be given in several courses in order to control recurrent pustular episodes.

Roentgen therapy, properly filtered and administered with regularity by an expert, has its place of usefulness in acne therapy.

Oral estrogenic therapy produces very favorable response in the control of acneform eruptions in certain patients.

The synthetic estrogenic substance chlorotrianisene has value in the dermatological armamentarium for the treatment of acne.

1219 Carew Tower (2).

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REHABILITATION IN INDUSTRIAL DERMATOSES

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IN THIS paper I should like to direct your attention to the socioeconomic aspects of the person who because of skin trouble is not contributing his full share to society.

Dermatoses account for approximately 65% of all cases of occupational diseases reported throughout the United States. In our experience in the State of Washington, even during the war years, when an unusually high incidence of respiratory irritation was reported as due to welding fumes in shipbuilding, occupational dermatoses held their own. From 1943 through 1948 there were an average of 1,300 occupational disease claims filed per year in this State, of which 55% were industrial dermatoses claims. California in 1949 reported over 12,000 cases of occupational disease, with 55% due to dermatoses.

From the fall of 1945 through the spring of 1949 I had the interesting challenge of studying all occupational disease cases reported in the State of Washington, in which there was a difference of medical opinion as to whether or not they should be compensable. Written opinions were prepared for the record on 288 cases. Only 34, or 12%, of these involved the skin, but I believe many more should have been questioned. Perhaps so few cases of dermatoses were questioned because of the lack of guideposts as to what constitutes an occupational dermatitis and the tendency of the insurance carrier to accept as an occupational disease without further investigation most cases so reported. Of the 34 skin cases studied, one-third after thorough study were considered to be of occupational origin. Another third were open to question, and the rest were felt to be nonoccupational. The questionable cases were chiefly those needing patch tests or other confirmatory diagnostic aids to complete the causal relationship—for example, the man working with sheet aluminum and suffering from a contact dermatitis reported as due to contact with aluminum. Obviously, the aluminum was not the causative factor. Were oils and greases contacted at work responsible, or was the dermatitis due to contact outside of employment? Another questionable case is that of the woman who while sorting soiled clothing in a laundry developed a paronychial infection. Was this of occupational origin?

Claims for diseases of nonoccupational origin included such cases as the shipyard worker whose furuncular dermatitis of the right thigh was reported as due to fumes from welding on galvanized metal. Another is the patient with fungous infection

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which began on the feet, extended up the legs, and became acute during the warm months of the year. This patient, a brick mason, was reported to be a victim of cement irritation; yet the hands and arms which were constantly exposed to cement products at work were free of lesions. Do not such claims indicate the need for more careful evaluation by the insurance carrier before determining whether a case should be compensable?

Conditions which have never before been considered occupational are now beginning to appear in industrial insurance claims, for instance, scleroderma, psoriasis, lichen planus, and lupus erythematosus. The patient with scleroderma was more uncomfortable when working in a refrigerator, and thus claimed cold has caused the disease. Psoriasis or lichen planus about to erupt may frequently make its appearance in a scratch, abrasion, or in an area subject to friction. If the friction or scratch is acquired on the job, question may arise as to the causal relation between the lesion and work. Such an industrially acquired scratch or friction could determine the time and location of the attack but could produce the disease only in the predisposed person. Without such predisposition the disease would not occur, regardless of the severity of the trauma. Are these then occupational diseases? Shall we compensate such patients for all future difficulty with psoriasis or lichen planus? How should the dermatologist report such cases, and what should his recommendations be? A similar situation occurred in the patient about to develop lupus erythematosus. He was working in the sun with creosoted poles, and, no doubt, sensitization occurred and became the trigger mechanism. However, as in psoriasis and lichen planus, without the predisposing factor the disease would not have occurred. Naturally, the patient wanted the lupus erythematosus to be declared an occupational disease. Do you, as a dermatologist, believe it should have been?

Another aspect of the dermatological problem in industry concerns job placement. We have in our society many on relief rolls, persons unable to work or not working because of some chronic or slowly progressive disability. Rehabilitation is concerned with getting such persons into gainful employment. A qualified physician of physical medicine, such as Howard Rusk, could quote many statistics to convince any doubting Thomas there may be among you that rehabilitation works and that it pays in dollars and cents. I will leave that approach to the experts, but I wish to point out that with a little extra interest and with a modest amount of coordinated effort of dermatologists, industrial insurance carriers, plant medical departments, and vocational rehabilitation personnel many people dependent because of chronic or recurrent skin conditions can be helped to become tax producers rather than tax consumers.

The State Division of Vocational Rehabilitation of each state and territory attempts to determine those physical, mental, or social factors which make it impossible for persons to secure and hold suitable employment. It tries to eliminate or modify those factors in order to enable the handicapped to fully utilize their potentialities. When the handicaps cannot be altered the persons are assisted to find their niches in the work world. Obviously, many vocationally handicapped persons are not good candidates for rehabilitation, and the worker in that field, with the aid of appropriate consultants, must select those cases which seem amenable. Thus, not all cases you refer to the rehabilitation worker can be rehabilitated, though from experience I can assure you that many will.

Vocational rehabilitation services are available to any person of working age (16 years or over) with a fixed or slowly progressive physical, mental, or emotional handicap. Any such person, regardless of his financial status, is eligible to receive educational advisory or placement services without cost. Applicants in financial need and unable to pay may be provided medical care, books, maintenance, transportation, and the tools of their new trades.

Many persons who have been inactive for long periods because of disability become emotionally insecure and financially dependent. Experience has shown that the person for whom vocational rehabilitation can do the greatest good is the recently ill or injured person whose attending physician knows he will not be able to return to his former job. If the physician refers such a patient to Vocational Rehabilitation while still caring for him, he can have assistance with getting him back to work, so that emotional disturbances, "compensationitis," "welfaritis," and other forms of dependency can be prevented.

Vocational rehabilitation is not a medical care program per se. The only conditions for which medical care are provided must be static or relatively stable, and there must be reasonable assurance that after such care the person will be employable. Vocational rehabilitation cannot provide medical care for the acute or subacute case of dermatitis, but in a chronic long-term case in need of other rehabilitation services treatment may be provided.

The dermatitis patient may need advice as to the kind of job he can safely do. The patient with contact dermatitis needs advice on how to protect himself from the causative agents, and if dermatitis occurs repeatedly even after reasonable efforts at control he might well be considered for a change of vocation where agents likely to offend will not be encountered. Patients with disfiguring dermatoses, such as acne, may also need help in securing satisfactory employment. The dermatologist's responsibility for patients with such cutaneous intolerance is to get them back to work at the earliest possible moment in a work situation where the dermatoses will not be a liability. Some of these persons may need extensive vocational counseling, guidance, training, and assistance with job placement, without which they may and often do become dependent upon society. There is a limit as to how far it is practicable for the dermatologist to go in this regard, but the Division of Vocational Rehabilitation in your state is in a position, on request, to provide these services to your patients and to make possible the gainful employment of many who on their own are unable to link up with employers looking for people with their particular assets. Rehabilitation workers and many employers are interested not in what the person has lost in bodily function or appearance and not in what he no longer can do but rather in what he has left and what he can do with what is left.

I will illustrate how Vocational Rehabilitation operates. Let us look for a moment at the 38-year-old auto mechanic whose skin developed a severe intolerance to petroleum products and who as a result lost considerable time from work and filed several industrial insurance claims. In attempting to find safe employment he leased a gasoline station. He felt he could get along there without difficulty but soon found he had made a mistake, and after other episodes of dermatitis for which he was uninsured he eventually lost his investment. This man was broken, discouraged, and though once proud was now resigned to letting the taxpayer support him and his family.

After two years on welfare with his wife and six children, the local welfare department, void of medical consultation, recommended he be placed on the rolls of the totally and permanently disabled in order that part of the cost of his maintenance would be shared by the federal government. The physician and vocational expert on the board reviewing cases for Total and Permanent Disability recommended referral of this patient to Vocational Rehabilitation. The patient, not too intelligent, quite satisfied to receive nearly as much for not working as he had ever earned, did not seem a likely prospect for rehabilitation. After careful counseling he revealed he had always wanted to be a barber. The challenge of barber training provided a fascination for him, and today he is again a proud and happy husband and father supporting his family rather than being a burden on the taxpayer.

Labor and management have been instrumental in development of state industrial insurance laws. No doubt the legislative intent has been to compensate for time loss and to provide medical care for the worker injured or made ill because of his work, but not to provide a broad health and accident policy for all covered workers. Too liberal interpretation of industrial insurance laws leads to many problems, some of which bear closely on the day-to-day practice of medicine.

In the State of Washington an occupational disease is defined as one which arises "naturally and proximately out of extrahazardous employment." The law provides that if a physician is requested by a worker to file an occupational disease claim he is obliged to do so. Claims filed in such circumstances are sometimes declared compensable even when in the opinion of the reporting physician the case is nonoccupational. Such things happen because of liberal attitudes toward the injured worker. It is the responsibility of our industrial insurance department to determine in each reported case of occupational disease whether or not it is compensable. The department is naturally influenced in such decisions by attitudes of physicians and attorneys with whom they deal, by the courts, and by labor and management. Extremely liberal decisions have sometimes been reached in cases that have been appealed to the Supreme Court. Such decisions have the power of law and influence future action of the insurance carrier in like cases.

Labor, often to the detriment of the very people it attempts to serve, at times strives unrealistically to get all it can for the injured worker in the name of fringe benefits and to lay all responsibility on the employer. Management, on the other hand, is often very philosophical about industrial insurance and its attitudes range from that of insisting they never had a case of occupational disease and fighting every claim to the limit to that of paying all claims, even though they know the case is not an occupational disease. These latter industries feel that what they lose in increased insurance premiums is offset by improved public relations which would suffer if they contested claims, however unreasonable or unjust such claims may be. This tendency to allow the unreasonable claims leads to laxness and makes industrial insurance a broad coverage health and accident policy. If industry is going to pay all claims and charge the costs up to public relations, why should the physician and the insurance carrier be critical as to the origin of the injury? To delve even deeper, is it possible that government-operated insurance carriers might be influenced in their decisions relating to occupational origin of injuries, by pressures from labor or management, depending upon which did the best job of getting their people in key governmental positions? These problems present a complex picture, and the remedy is not simple but should be intelligently approached.

In dealing with problems so basically medical, are we as physicians going to confine ourselves to diagnosis and treatment or are we going to exert our influence so that the socioeconomic aspects of these problems are decided on a basis of sound medical judgment?

Throughout the years that I served as consultant on occupational diseases to the industrial insurance program in the State of Washington, cases of industrial illness, including dermatoses, were not reported as occupational diseases, often with considerable economic loss to the patient. More frequently, however, illness bearing no causal relationship to employment was reported as occupational. All too often in government-operated industrial insurance programs these original reports are accepted as prima facie evidence, and compensation is granted. Should not State government investigate all reported cases of occupational disease, compensate through industrial insurance only for those that are of industrial origin, and provide machinery for preventing further cases wherever possible?

Perhaps a policy as to when a case of occupational disease should be terminated is needed. For example, take the case of atopic eczema which flares up as a result of exposure to an irritant at work. You have all seen these, where you have felt certain the patient has a long history of disease, yet in attempt to get compensation benefits he says this is his first attack. If this case is considered to be compensable where do you draw the line? Such cases may persist or recur. Does the insurance carrier treat the eczema the rest of the patient's life? Secondary factors, such as soap and water in the dishpan at home, may aggravate the eczema flared up by the irritant at work. Poison ivy in a vacationer does not last forever. How long should it last if acquired in line of duty and declared an occupational disease?

How about the patient whose skin is highly sensitive to paint solvents and whom you have repeatedly told to stay away from them after he has encountered difficulty on the job? Even while on time loss he paints his house or repairs the car and washes parts in paint solvent. Should industry support him on time loss indefinitely? Should the insurance carrier, even in the absence of any future industrial exposure, accept each new outbreak of the dermatosis as an aggravation of the original occupational disease? Perhaps in such cases some rules should be set down. If so, what will they be?

The goal for control of occupational diseases is reasonable, and the technology or "know-how" for their prevention is available. The costs of such a program are far less than the hidden costs of industry compensating for damages for which it is not responsible. The philosophy of industrial insurance is to afford the worker protection against marked economic loss due to industrial injury. Unless industrial insurance works, it becomes a general health and accident insurance operating under an assumed name paid for by one segment of the population for the benefit of another segment.

I have seen many people, some, incidentally, with nonoccupational dermatoses, who were unquestionably capable of earning a living but because of unintelligent handling were allowed to become totally dependent. Having an occupational disease which they believe incurable they develop "compensationitis," and after the compensation has run out, "welfaritis." If time permitted I could cite case after case of persons with silicosis, low back pain, eczema, and other diseases related to indus-

trial exposure, who have needlessly been made a burden on the tax payer. Such waste can be prevented, and the cost of prevention is much less than the cost of continued neglect.

Another dangerous pitfall in industrial insurance is the practice of salaried lay people interpreting medical results. The medical profession should take sufficient interest to assure that medical decisions relating to industrial insurance will be made only by physicians.

It would appear feasible to have a rotating panel of qualified practicing physicians meeting at a given time and place to consider industrial claims. Such panel, instead of meeting hastily at lunch to discuss a single case, would have the advantage of the complete files of several cases and could at a single setting complete them. Decisions of these panels should be accepted as final and not open to review. This would seem entirely fair, less expensive, and more convenient to the physician than the present system of commission examinations, which, unfortunately, are frequently reversed by a lay employee of the state or by the courts. Such a panel would also be in a position to declare these problem cases occupational for the acute episode only or for a reasonable length of time. Perhaps some standards could be made applicable by the panel, such as that the work is only 20% responsible for a given condition. Maybe after two or more dermatitis attacks related to work a change of employment should be mandatory, or perhaps the patient should be refused further industrial insurance benefits if he fails to protect himself. Such a panel could certainly give impartial scientfic answers to many questions left unanswered with our present method of operation.

What can you as dermatologists do to check the widespread misuse of industrial insurance as a double for health and accident insurance?

To attack these problems intelligently, I believe a teamwork approach is necessary. The team should be made up of the medical profession, labor, management, government, and insurance carriers. Should the physicians who see these problems daily take the lead in organizing such a team? What do you think?

ABSTRACT OF DISCUSSION

DR. MAXIMILIAN E. OBERMAYER, Los Angeles: Dr. Farner has raised a goodly number of important questions as to the management of persons with industrial dermatoses. It will be well for all of us to ponder them and to attempt to supply adequate answers. Both constructive and timely is his suggestion of a rotating panel of practicing physicians–specialists in their respective fields, may I advise–to consider the individual merits of industrial claims and to promote utilization of newly determined scientific facts in the handling of particular cases; it deserves serious consideration by State authorities.

I was much impressed with this report on rehabilitation. While Dr. Farner has pointed out the many-faceted nature of the problem of industrial dermatoses, an additional aspect–that of the psychic component–must also be stressed.

The coexistence of emotional factors in occupational disease, especially in large industrial plants, is one of the most difficult problems encountered. The patient on whose skin an inflammatory eruption appears while he is at work automatically assumes it to be due to some factor connected with his occupation, particularly if the disorder may be classed in a compensable category. Although some patients are malingerers, others are not. A large proportion–perhaps the majority–of cases of "industrial dermatitis" are actually cases of chronic-recurrent dyshidrosis or neurodermatitis of the hands. Accurate diagnosis is of the utmost importance to the worker, the industry, and the community. True industrial dermatitis is, almost always, contact dermatitis. Successful methods of desensitization of the skin have not yet been devised; hence the patient's return to identical working conditions after disappearance of his dermatitis almost

invariably is followed by its recurrence; if not, the diagnosis may have been incorrect. On the other hand, should the eruption disappear during absence from work and again develop on return to work, this sequence usually is accepted as indubitable evidence of an occupational cause. But any ailment is likely to improve during a period of rest; even though the patient is fatigued due to anxiety and/or emotional imbalance, discontinuance of the regular daily task often affords sufficient relief to bring about improvement or involution of the dermatitis.

Associated social, occupational, and emotional disturbances seem to be integral to, if not the cause of, many cases of industrial dermatitis. Psychosomatic manifestations may predominate, and the disorder often is indistinguishable from an occupational neurosis. In some instances, it has seemed obvious that the cutaneous disorder would have occurred regardless of a sensitizing factor. Often the patient with chronic-recurrent industrial dermatitis harbors a sense of injustice; his personality may be described as socially inadequate obsessional; he is reserved and shy and feels inferior and inadequate; he fears both punishment and insecurity. An alleged industrial dermatitis will enable an aging craftsman to change, without loss of face, to a much less exacting job; his social and economic descent thus is attributed not to his own deterioration or disinclination, but to working conditions, often eventuating in enjoyment of a sense of grievance. In such a case, if the diagnosis of industrial dermatitis is in error, the situation becomes even more deplorable: The harder the patient tries to convince himself of the validity of the diagnosis, the more strongly and aggressively does he cherish his perverse belief. Those with occupational cutaneous neuroses resemble, to some extent, persons with factitial dermatitis; both desire to prolong their disorders, the former by exaggerating subjective symptoms, the latter by actual self-excoriation.

The need for psychiatric study of industrial patients with unduly protracted dermatoses is very real. In addition to the routine inquiries, questions must be directed at the worker's reaction to (1) the type of work, (2) the mental and physical effort required, and (3) his fellow-workers and superiors.

A sound working knowledge not only of the common diseases of the skin but also of industrial problems, working conditions, and an insight to human relations within industrial spheres is essential to the physician who deals with industrial dermatoses. If strong deviations of personality are evident, the patient should be referred for psychiatric consultation, because an inept, direct attack on the psychologic aspects of the dermatitis, on a purely intellectual level, would create havoc in such poorly integrated personalities.

As Dr. Farner has indicated, both workers and employers will benefit from enlightened management of occupational dermatoses, which necessarily includes appreciation of psychologic factors in the production of dermatoses. The situation prevailing in some industries is deplorable; for example, the physician on the premises may make an indiscriminate diagnosis of industrial dermatitis which then may be reversed, equally indiscriminately, by the physician for the insurance carrier; this common occurrence breeds discontentment and a sense of grievance in the patient.

I should like, therefore, to augment Dr. Farner's excellent proposal for a rotating panel of practicing physicians to review industrial cases: (1) by stipulating that the roster include specialists in the medical fields represented by the manifest organic disease, and (2) that it be mandatory that the panel include a dynamically oriented psychiatrist, who would serve as a guarantor that possible psychologic considerations will not be ignored, thereby assuring not only that neither employer nor insurance carrier be mulcted, but also that rehabilitation of the patient may be based on sound psychologic principles.

HALLOPEAU'S COMMUNICATIONS ON LICHEN SCLEROSUS ET ATROPHICUS

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THE ORIGIN of the lichens is lost in dermatologic antiquity. The earliest books on skin diseases (e. g., those of Willan and of Bateman) contain chapters on this group. Through the years numerous investigators have described a wide variety of unrelated dermatoses by using the term lichen plus one or more qualifying descriptive adjectives. When Erasmus Wilson isolated lichen planus in 1868 he "separated this entity from a chaotic group," as Graham Little said in an address delivered in 1919 at the American Dermatological Association meeting.

After lichen planus (or Wilson's lichen, as it became known on the European continent) and its clinical forms became universally recognized as a distinct entity, attempts were made by authorities to limit the use of the term lichen to this particular disease. Fred Wise, for example, in a well-written article published in 1919, called "Neurodermatosis and the Pseudolichens," made an eloquent plea for this simplification in our dermatologic terminology. "The neurodermatoses are not lichens, despite the fact that an occasional example of lichenification will so closely simulate lichen planus that the resemblance between them is far stronger than their difference. Let the name lichen be used exclusively for lichen planus with its large family," he said at that time. A few of the lichens have become obsolete. Dermatologists no longer speak of granuloma annulare as lichen annularis, for instance. However, despite these attempts at limitation, most of the dermatoses that were described by the word lichen have retained their original names.

In the present state of our knowledge, the lichens may well be divided into three classes: (1) lichen planus and its clinical forms; (2) those dermatoses which are obviously not lichen planus (for example, lichen chronicus simplex, and lichen urticatus), and (3) those dermatoses about which doubt existed or still exists concerning their true relationship to lichen planus.

In this last group, one finds lichen sclerosus et atrophicus. Since this rare condition was first described by Hallopeau, in 1887, a voluminous literature has been built up. Many papers have been written by a number of authors, who have described the same, similar, or allied conditions under different morphologic terms which are often confusing and bewildering. A partial list of the names which define either this condition or one of its variants includes the following: lichen albus of von Zumbusch, dermatitis lichenoides et chronica atrophicans (Csillag), lichen

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planopilaris (Pringle), folliculitis decalvans et atrophicus (Little), lichen planus et acuminatus atrophicans (Feldman), folliculitis decalvans et lichen spinulosus, *lichen planus scléreux keloidiformis (Pavlow)*, lichen planus seu spinulosus, *folliculité déstructive des régions vélues (Quinquad)*. In 1941 Ellis listed no less than 20 different names. In a recent article by Silver, Chargin and Sachs on lichen planopilaris, attention is called to the fact that some 30 titles have been used to describe similar dermatoses.

A wide divergence of opinion exists among dermatologists as to which of these terms refer to varieties of lichen planus and which ones describe separate, distinct entities; one need only read the discussion that follows when a case is presented at a dermatologic society meeting.

Because of the large number of articles that have been written about this uncommon dermatosis, it should be worth while to look back and examine Hallopeau's own original communications on this subject, of which there were four.

Hallopeau's original case was contained in a clinical lesson on lichen planus which was given to students when he was appointed to a teaching position at the Hôpital St. Louis in Paris; it was published in 1887 in the *Union Médicale*. The author called his case a variety of lichen planus and he gave it the name "lichen planus atrophicus" *(lichen plan atrophique)*. An abstract was contained in one of the numbers of the *Annales de Dermatologie* of the same year. In the abstract, mention was made of the fact that Darier had made the histologic examination.

The second article appeared in the *Annales de Dermatologie* in 1889. It was called "lichen planus sclerosus" *(lichen plan scléreux)*. It consisted of a case presentation at the weekly clinical conference of the *Société Française de Dermatologie*. Along with this second case a moulage of the first case (the subject of the clinical lesson in 1887) was shown to demonstrate the resemblance. Hallopeau explained that he was using the term sclerosus rather than atrophicus because Darier had suggested that the former more accurately described the histologic changes. He thought he was dealing with a special form of lichen planus in which the elements were "pale and discolored" from the very beginning (i. e., the lack of color was not due to a terminal achromic transformation of typical lichen planus papules).

The third article was published in 1896 in the same journal. This was also a case presentation at the same society. It was called "another case of lichen planus atrophicus." At the end of his description of the case, Hallopeau said: "The sclerous and atrophic characters distinguish it from ordinary lichen planus and we may ask whether we are dealing with the same dermatosis." This patient, however, had typical lichen planus lesions in the mouth. The author terminated his presentation with five conclusions:

1. Lichen planus atrophicus is seen most frequently on the anterior aspect of the distal end of the forearms.

2. There may be mouth lesions and therefore we are dealing with lichen planus.

3. We should not add the word "ruber" because the lesions are never colored. (We must remember that lichen ruber planus is used as a synonym of lichen planus.)

4. The lesions may look like morphea.

5. The initial lesions of lichen planus are found most frequently at the glandular orifices. This is where the parasite should be sought.

The fourth article was published in 1898 in the same journal and it was still another case presentation at the same society. The title of this article was called "*Lichen de Wilson scléreux.*" Hallopeau raised the following point:

A fact worthy of note, already mentioned several times, and which is the rule in this form of lichen, is the complete absence of colored elements. In the presence of such a dermatosis, we may ask if we are not dealing with lesions which were from the beginning sclerous and achromic or whether we are dealing with a regressive transformation of elements of Wilson's lichen. The facts favor the first interpretation, for if it were otherwise, we would see ordinary lichen planus papules during the early phases of the disease, but this is not so.

In 1900, Hallopeau wrote a textbook on dermatology in collaboration with Leredde. Under the clinical forms of Wilson's lichen there was a description of the sclerous variety which had "all the characteristics of lichen planus except the red color and the relief."

It should be noted that in all four of his communications Hallopeau presented a case which he believed to be a clinical variety of lichen planus. In the discussions which followed the presentation of these cases, none of the members of the French Dermatological Society disagreed with the opinion of the presenter. It may also be pointed out that this is still the prevailing opinion of French dermatologists.

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TRICHOPHYTON TONSURANS INFECTION IN TINEA CAPITIS SURVEY

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THIS STUDY of childhood tinea capitis in the largest city of Arizona (Phoenix) was stimulated by a search of the literature which failed to reveal the incidence or indeed the occurrence of infections caused by the organism Trichophyton tonsurans in this area. Pipkin, in his classic paper, stated that he received reports of two cases of favus in adults who resided in this state, but infections due to other endothrix fungi were not mentioned. The reports from various observers in Texas, including Pipkin, Seale (personal communication), Walton, Livingood, and Mullins (previous work and statistics at the University of Texas School of Medicine), recorded a relatively high incidence of T. tonsurans scalp infections in that state. The experience of Wilson (cited by Pipkin) in Southern California indicates that there is a similar relatively high incidence of this type of infection in that part of the country. It is agreed that the number of such infections is increasing in the Southwest and on the West Coast, and it would seem probable that one would expect to find patients with endothrix scalp infection in the neighboring states. There is reason to believe that this organism is tending to extend to the United States from Mexico, where the incidence of T. tonsurans may be as high as 92% (Gonzalez Ochoa, cited by Pipkin). Georg, of the United States Public Health Service, is of the opinion that the increase in the number of cases caused by T. tonsurans constitutes a new public health problem.

It is not the purpose of this paper to summarize all of the laboratory and clinical data regarding T. tonsurans, which are quite voluminous, but some of the salient features should be mentioned. When this infection is in an early or static stage, it may not be apparent, even to an experienced observer. On examination of the scalp, a mild scaliness may be present, and the classical "black dots" may be seen; i. e., the hairs are broken off flush or slightly below the surface of the scalp. Frequently, it is essential to "dig out" the broken-off stubs for KOH preparations and cultures. In other cases, the clinical manifestations may be that of folliculitis, furunculosis, or true kerion formation. This type of ringworm does not tend to clear up spontaneously at puberty as is the case with Microsporum audouini infections. T. tonsurans infection has been reported in three successive generations of the same family, and, on several occasions, I have observed the disease in both mother and offspring. Except in isolated cases, the Wood's light examination shows no fluorescence; if this test is positive, the fluorescence is not the typical bright greenish color of M. audouini and M. lanosum infections. In children, the incidence is about the same in both boys

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and girls, but in adults it is much more common in women. Microscopic examination of a KOH preparation of the hair stub infected with T. tonsurans shows the spores to be within the hair shaft (endothrix) in contrast to the external (ectothrix) position of M. audouini, M. lanosum, and M. fulvum. The cultural characteristics on Sabouraud's medium are quite distinctive for the various types of T. tonsurans. In the cases herewith reported, cultural growth was noted within a period of seven to eight days. The cultural mount with lactophenol blue revealed many microconidia en thyrses, chlamydospores, and few macroconidia.

METHOD

The seven schools selected for this survey were located in an area which houses a large portion of the lower income group of this city; 85.9% of the students in these schools were of Negro or Latin-American parentage. This locality was selected because there is a greater tendency for migration in this group, and the overcrowded living quarters should promote the extension of the infections. These two factors seem to be important in the spread of tinea capitis from one locality to another as well as from person to person.

A total of 3,365 children, between the ages of 6 and 12 years, were screened closely by the teachers and school nurses for any type of skin or scalp lesion. In this manner, a total of 502 children with skin and/or scalp lesions were selected for careful examination, which I carried out. Wood's light examinations were done in all cases, and hairs were taken from all suspicious sites of involvement; the usual KOH examinations and cultures were done in all cases.

Tabulation of Etiologic Organisms

	No. Pupils Screened and Examined	No. Cases T. Capitis	No. Cases M. Lanosum	No. Cases M. Audouini	No. Cases T. Tonsurans (var. Sulfureum)
No. 1 (L. A.*)	580	4	4	..	..
No. 2 (Negro)	565	10	6	2	2
No. 3 (Negro)	430	7	6	..	1
No. 4 (L. A. and white)	417	1	1	..	..
No. 5 (L. A. and white)	398	6	5	1	..
No. 6 (Negro)	428	2	2	..	..
No. 7 (L. A.)	547	2	2	..	..
	3,365	32	26	3	3

* L. A. = Latin American.

RESULTS

As shown in the Table, 32 of the 3,365 children were found to have tinea capitis; M. lanosum was cultured in 26 cases, M. audouini in 3 cases, and Trichophyton tonsurans (var. sulfureum) in the remaining 3 cases. T. tonsurans was found in two girls and one boy; these three patients were Negro children. Two of the infections were the dry, scaly, "black dot" type, and the other patient presented a boggy kerion lesion. Percentage-wise, there was an equal distribution of M. lanosum and M. audouini among the Negro, the Latin-American, and the few Caucasian children who were included in the survey. The three patients with T. tonsurans infection had lived in Phoenix during their entire lifetime; no other members of the families of these children were found to have the disease. During the observation period of four months, the male child had a complete cure without an inflammatory reaction. This was thought to be due to a spontaneous immunological response on the part of the patient rather than the fungicidal effect of the therapeutic agent which was applied.

SUMMARY AND CONCLUSIONS

A preliminary screening examination done by school nurses in each of 3,365 school children of Phoenix, Ariz., revealed 502 children with some type of skin and/or scalp lesion.

Examination (including Wood's light, KOH, and mycologic cultural studies) resulted in the positive identification of tinea capitis in 32 children; this represents an incidence of approximately 0.9%.

Twenty-six, or 81.2%, of these cases were due to M. lanosum, 3 or 9.4% were due to M. audouini, and 3, or 9.4%, were due to T. tonsurans (var. sulfureum).

Experience which has been accumulated in other parts of the Southwest and West, particularly Texas and Southern California, would seem to indicate that in the future one would expect an increased incidence of T. tonsurans infections in other parts of the country, especially in adjoining states.

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MYCOLOGY, BACTERIOLOGY, AND HISTOPATHOLOGY OF SUPPURATIVE RINGWORM

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SUPPURATIVE ringworm includes all types of ringworm which attack the deep layers of the skin and hair follicles with the production of nodules and pus. Clinically the lesions are characterized by nodules or large boggy masses that arise abruptly from the surrounding tissue. They are angry red in color and dotted over with perifollicular abscesses. The hairs in these follicles are either lusterless and broken, or are shed completely, leaving gaping holes containing purulent fluid. The neighboring lymph nodes are usually enlarged. The lesions are known by various terms, depending on the site of the human body that is infected. If the scalp is infected, the lesion is known as kerion celsi (Fig. 1); if the beard area is involved, the diagnosis is tinea barbae or sycosis parasitaria (Fig. 2); and if the glabrous skin is affected, the terms used are agminate folliculitis or tinea profunda. The early lesion may be a flat plaque with an impetigo-like surface (Fig. 3).

In 1934 Davidson, Gregory, and Birt pointed out that the lesions on various parts of the body are essentially the same, and suggested that they be known by the comprehensive term of suppurative ringworm. While this inflammatory type of lesion has been recognized since the time of Celsus, it still presents many aspects that require clarification.

The deep inflammatory type of ringworm can be produced by Microsporum lanosum, Microsporum gypseum, and Microsporum audouini. However, the great majority of cases are caused by infection with fungi of the genus Trichophyton contracted from cattle. Until recently Trichophyton mentagrophytes (gypseum) has been recognized as the common cause of suppurative ringworm in North America. In 1925 Burgess in Montreal described one case of tinea barbae and one case of tinea circinata due to Trichophyton faviforme out of 99 cases of fungous infections of the scalp, beard, and glabrous skin. In 1934 Davidson, Gregory, and Birt reported a series of 46 cases of suppurative ringworm, 28 of which were caused by T. faviforme (album), and in 1938 Gammel and Work reported the first isolation of T. faviforme (album) in the United States. Since 1947 Fowle and Georg in an excellent article, Carney, and Jillson and Buckley, and Fischer and Wrong have reported series of cases of suppurative ringworm contracted from cattle. In

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Fig. 1.—Kerion celsi, showing large boggy mass arising abruptly from surrounding tissue.

Fig. 2.—Tinea barbae, with large boggy mass, partial loss of hair, lusterless hairs, and small follicular pustules.

all these reports by far the commonest fungus recovered was T. faviforme. It is becoming evident that this fungus is a very important cause of pustular ringworm in North America.

During the past 15 months we have observed a series of 30 patients with suppurative ringworm contracted from cattle. Thirteen had kerion celsi; 3 had tinea barbae; 10 had agminate folliculitis, and 4 had more than one area of the body involved. In this series we obtained 20 positive cultures, which will be discussed later. In the remaining 10 cases, 5 had microscopically positive hairs and negative cultures, and in 5 we were unable to demonstrate the fungus microscopically or by culture. Most of the authors quoted previously have had difficulty in isolating T. faviforme consistently. Gregory, in our original communication, was able to

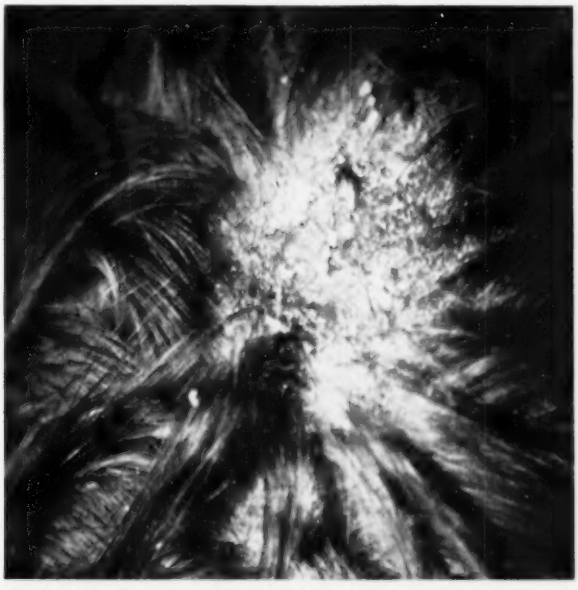

Fig. 3.—Early crusted plaque on scalp simulating impetigo contagiosa. Within a few days this lesion developed into a typical kerion celsi.

isolate T. faviforme (album) in only one-third of the cases in which he had previously demonstrated the large ectothrix spores of the faviform group microscopically. Fowle and Georg in their series of 23 cases of suppurative ringworm reported 5 cases in which no parasitized hairs were observed and in which no cultures that were positive for fungi were obtained. Carney was unable to demonstrate fungi in 7 of the 39 cases he reported.

The incidence of positive microscopic preparations and cultures is directly proportional to the care taken in selecting hairs and skin scrapings; this cannot be stressed too much. The isolation techniques used also influence the results, particularly in dealing with the slow-growing T. faviforme. The best hairs for examination are the lusterless, broken ones which can be extracted easily or hairs covered with crusts and centered in pustules. Filtered ultraviolet light is of no value in selecting the specimens.

Difco media has been used throughout this project. Sabouraud dextrose agar was used initially but it did not control the growth of contaminants. Then Littman oxgall agar was tried. One plate was incubated at 25 C. after inoculation, and one at 37 C. The second plate contained 1 mg. of thiamine hydrochloride per 100 ml. of medium. Littman oxgall agar controlled the growth of contaminants well. However, it also inhibited the growth of T. faviforme, particularly in skin scrapings. The growth of T. faviforme on hairs was inhibited to a lesser extent, and when it occurred was very characteristic of this genus. At the present time material is being cultured on Littman oxgall agar at 25 C. and on Sabouraud dextrose agar with 10 mg. of the antibiotic cycloheximide (Acti-Dione*) per 100 ml. of medium at 37 C. The final identification is made on Sabouraud dextrose agar at 25 C.

The cultural studies in our series of cases have been most interesting. During the first year 19 patients were examined, and nine positive cultures were obtained as follows: six Trichophyton mentagrophytes, two Trichophyton tonsurans, and one Microsporum gypseum. In the past three months, 11 patients have been examined and all have yielded positive cultures of T. faviforme. In retrospect, it seems probable that at least some of the 10 cases in which we failed to obtain positive cultures last year were caused by T. faviforme, and that our recent increase in positive results is due to experience gained in handling this slow-growing fungus. We hope to establish the actual prevalence of this organism in Manitoba by collecting a larger series of cases.

We have assumed for many years that the pus produced in ringworm was due to fungi. Crocker, as early as 1903, in a description of tinea barbae said, "This suppuration may be, and at commencement generally is, solely due to the pyogenic character of the fungus itself, but sooner or later pus cocci invasion occurs." Sulzberger speaks of "pus-forming fungous diseases." However, in most standard textbooks of dermatology there is no suggestion as to what produces the pus in ringworm. Certainly there seems to be an assumption amongst many of our confreres that the pus is due to bacteria; and there is an increasing tendency, particularly in rural practice where most of these patients are seen, to treat pustular ringworm with intensive antibiotic therapy. Because this type of therapy is usually expensive and carries with it the possibility of severe adverse reactions, a bacteriological study was made of some of our material.

The punch biopsies taken for histological examination were sufficiently deep to allow pus to exude from the resulting skin defect. This fluid was collected aseptically from 10 cases and cultured for bacteria. The media used included nutrient broth, fluid thioglycollate, and blood agar.

Bacteria were not recovered from any of the cases. This would indicate that the suppuration was related to the presence of fungi in the tissue. As it will be demonstrated later, the location of the spores and hyphae in the hair follicles and their absence in the dermis would support the contention that the inflammatory reaction which is so marked in the dermis is allergic in origin.

The histopathology of suppurative ringworm is not well recognized. Sabouraud, in his monumental treatise, "Les teignes," gave a most complete illustrated description of the histopathology of this condition. However, most modern textbooks omit it completely and do not consider it in the differential diagnosis of the cutaneous

* Acti-Dione was supplied by Upjohn Company, Kalamazoo, Mich.

granulomata. Laymon in 1946 described the lesions very minutely without illustrating them, and such authorities as Lever, and Becker and Obermayer mention the microscopic findings briefly. It would therefore seem justifiable to describe the histopathology of this granulomatous condition again. Material for histologic

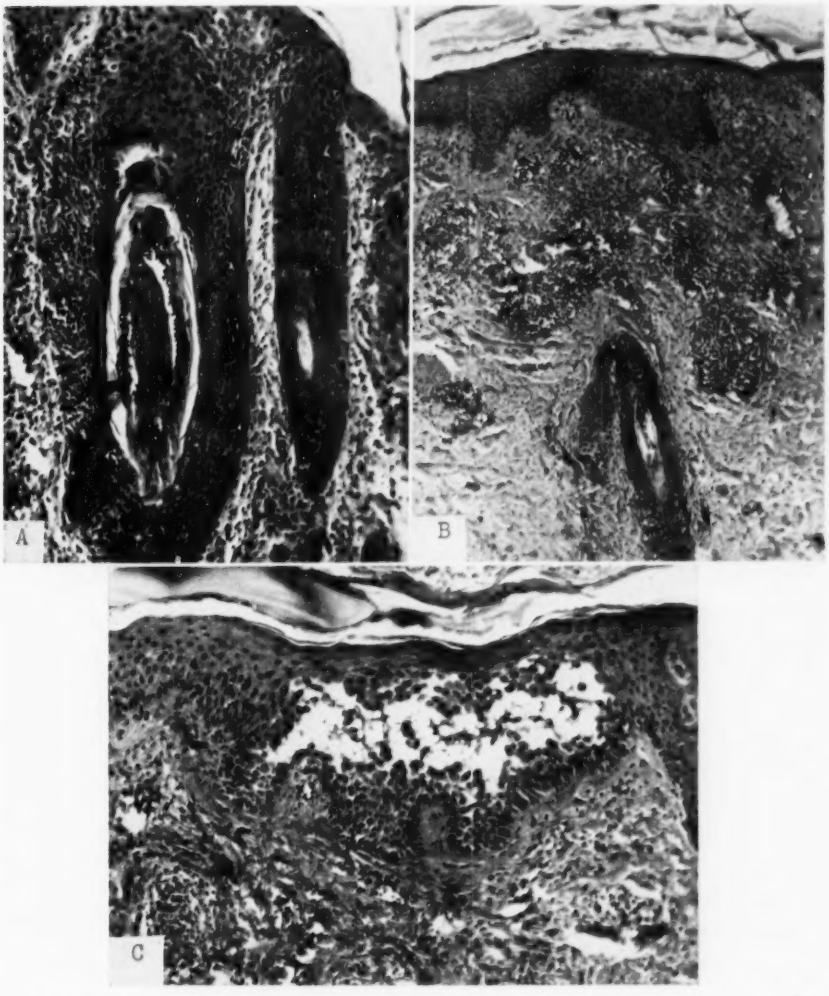

Fig. 4.—*A*, hair follicle with spores in the lumen and hyphae in the inner layer; × 125. *B*, early lesion; reaction confined to the superficial dermis around the hair follicles; × 60. *C*, intraepidermal edema; × 110.

examination was obtained from 10 patients by punch biopsy without the use of any anesthetic. The tissue was fixed in 10% formalin, embedded in paraffin, and serially sectioned. Sections were stained with hematoxylin-eosin, and with the periodic-acid-Schiff's reagent.

The periodic-acid-Schiff's reagent was very useful in identifying the location of fungi in the sections. Spores were seen within the hair shaft and in the lumen of the hair follicle. Hyphae were present in the inner cornified layer of the follicle (Fig. 4*A*). Despite an intensive search throughout the section, no fungi were found elsewhere. The hair in the involved follicle showed varying degrees of degeneration. Where complete degeneration had occurred, the follicle in many cases contained numerous polymorphonuclear leucocytes.

The histologic picture varied considerably in different cases. The epidermis was involved in all. In early lesions inflammatory cells were confined to the superficial dermis and surrounded the hair follicles (Fig. 4*B*). The cells consisted of lymphocytes and polymorphonuclears in about equal numbers. Some intraepidermal edema was evident, together with prolongation of the rete pegs (Fig. 4*C*).

In well-established lesions the reaction was complex, involving the epidermis and the dermis to the deepest part of the section (3 to 4 mm.) (Fig. 5*A*). The inflammatory cells were predominantly plasma cells with a few scattered lymphocytes, large mononuclears, and polymorphonuclear leucocytes (Fig. 5*B*). Collections of polymorphonuclear leucocytes (microabscesses) were seen throughout the dermis. In some cases numerous eosinophiles were present in the deeper parts of the tissue. Collections of three to four giant cells of foreign body type, with a few epithelioid cells, were found throughout the dermis in some instances (Fig. 5*C*).

The epidermis in these advanced cases was edematous, with prolongation of the rete pegs; in one case epidermal changes were sufficiently marked to simulate pseudoepitheliomatous hyperplasia (Fig. 5*A*). A number of microabscesses were seen within the rete pegs (Fig. 5*D*).

It would seem that the initial phase is the extension of the fungi down the hair shaft with invasion of the inner layers of the follicle. The first reaction to this is simple and confined mainly to the superficial dermis and around the appendages. The next stage is the extension of this process throughout the dermis, the infiltrate being made up predominantly of plasma cells. Finally the entire dermis is involved in a granulomatous type of reaction with localized microabscesses. The abscesses must tend to coalesce to give rise to the large collections of pus that are so evident clinically.

SUMMARY AND CONCLUSIONS

Suppurative ringworm, contracted from cattle, is a relatively common infection in rural Manitoba. Clinically the lesions are typical, but it is often difficult to confirm the diagnosis mycologically. Great care is necessary in selecting the proper hairs for examination, and experience with the vagaries of slow-growing Trichophyton faviforme is required to obtain confirmation of the clinical diagnosis in a high percentage of cases. It is becoming increasingly evident that T. faviforme is a very common cause of suppurative ringworm in North America. The pus present is a result of the allergic reaction of the tissues to the fungus, and bacterial antibiotic therapy is not indicated. An increased awareness of the variegated histopathological response in this condition is of value in the consideration of the differential diagnosis of the cutaneous granulomata.

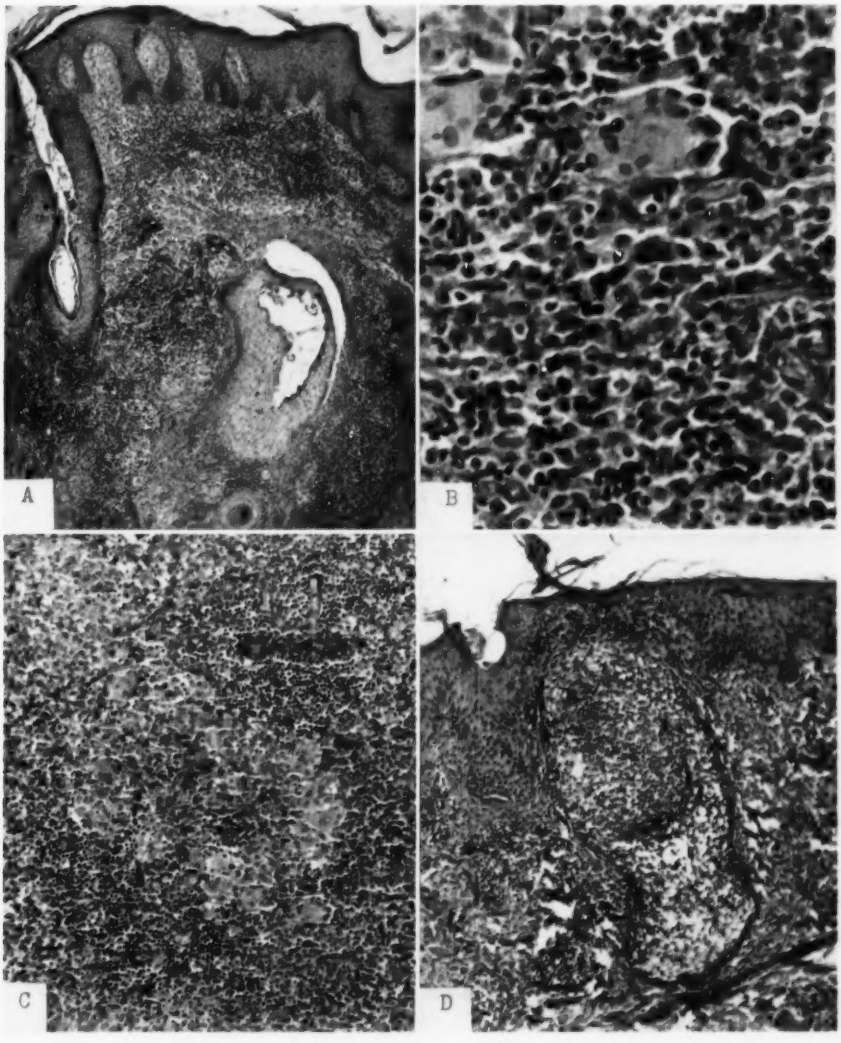

Fig. 5.—*A*, well-established lesion with extensive infiltration of dermis; epidermis shows considerable hyperplasia; × 40. *B*, inflammatory cells of the dermis; predominantly plasma cells with scattered lymphocytes, large mononuclears, and polymorphonuclear leucocytes; × 400. *C*, a collection of epithelioid and giant cells in the dermis, surrounded by plasma cells and lymphocytes; × 110. *D*, a microabscess within an enlarged rete peg; × 75.

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LOCALIZED CHROMIDROSIS

A Survey

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I have a couple of other rarities to present to the Royal Society, one of which is matchless, and to me wholly new.

A girl in Plymouth, 16 years of age, had about the end of April a few hot pimples arise on her cheeks, which bleeding and a purge or two cured. She continued very well till about a month after, when her face suddenly turned black, like that of a negro. This surprising accident much frightened the girl, even to distraction, when my assistance was required. By the arguments I used, and some composing anti-hysterical remedies, the violence of her fits were much abated. I also directed a lotion for her face, which took off the discolouration, but it returned frequently, though not regularly, sometimes twice or thrice in 24 hours, sometimes five or six times. It comes on insensibly, without pain, sickness or any symptoms of its approach, excepting a little warm flushing just before it appears. It easily comes away, and leaves the skin clear and white, but smuts the cloth that wipes it from the face; it feels unctuous, and seems like grease and soot or blacking mixed. It has no taste, which seems very strange, that a fuliginous exudation should be insipid.

She never had the menses, is thin, but healthful; the blackness appears nowhere but in the prominent part of her face.

The anomalous blackness of the girl's face is now divided into a few dark, cloudy specks, which appear but seldom, and nothing so livid as formerly.

IN THIS brief note to the Royal Society of London, in 1709, James Yonge, of Plymouth, England, recorded a case of chromidrosis. Although preceding accounts had appeared in the Middle Ages and possibly earlier, Yonge's description has been universally accepted as the definitive classic. Sporadic cases appeared in the medical literature of the remainder of the 18th and the first half of the 19th century. Prior to the year 1850 the entire body of information was to be found in eight reports.

However, the period of 1850 to 1865 saw an intensive and exhaustive study of the problem of chromidrosis. Disputations and arguments arose out of the 45 communications which appeared during that 15 years. Le Roy de Méricourt, a French professor of Naval medicine in Brest, was the central figure of this vigorous

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medical polemic. His opposition maintained stoutly that chromidrosis could readily be explained on the basis of dissimulation and artefact. Through persistent and careful studies de Méricourt gradually won the field. During this period it became apparent that true localized chromidrosis did occur, although cases of pseudochromidrosis were found in persons attempting to deceive by the external application of dyes. Le Roy de Méricourt gave the abnormality its present name, and his observations on nine patients with chromidrosis served as a basis for an exquisite monographic review of the entire field.

There were 38 recorded cases of localized chromidrosis by 1869. The following is a summary of the significant clinical findings and etiologic views of that time:

Fig. 1.—Chromidrosis in a patient described in 1845. This illustration was taken from a lithograph in the original article. The patient was 15 years old when she first noted this brown-black secretion. Because of tenderness of the involved skin, removal was never attempted by the patient. This water-color drawing shows a two-day accumulation of the secretion on the right side of her forehead and a five-day accumulation on the left. Note chromidrosis of the lower eyelids also.

1. Chromidrosis usually occurred symmetrically on the face of young women (Fig. 1). Thirty-four of the cases had been in women. Most frequently it had been seen on the lower eyelids but commonly had occurred on other parts of the face. Less frequently it appeared on the chest, abdomen, and thighs. The age range of the patients was from 15 to 57 years, the mean being 22 years. No common denominator of class or occupation could be found. These patients generally were in good health.

2. In the majority of instances the color was black or very dark. Twenty-one of the persons had shown black or brown discoloration, 15 blue or violet, and 2 yellow.

3. The color appeared intermittently, sometimes as often as six times a day and other times at long intervals. At times it would appear during sleep. It was preceded by prickling or a warm sensation. Emotional stimuli, such as anger, fear,

agitation, and laughing, caused the secretion. Usually the problem was severer in the summer. In at least one instance the condition improved during lactation. It persisted indefinitely in some persons, the intensity and amount varying from time to time.

4. A viscid liquid secretion was seen initially. This would dry rapidly to form an adherent glistening cap, usually at the hair follicle or sweat pore. Several observers described the dried secretion as having the appearance of dried varnish. The skin underneath was normal.

5. No microscopic examinations of the skin were made, but chemical studies of the pigment deposited on the skin led to the following issues:

(*a*) There was general agreement that the pigment was amorphous, contained carbon and iron, and was soluble in acids, especially sulfuric, and insoluble in water, alcohol, or ether.

(*b*) There was dispute over whether or not the pigment was melanin, indigo or indican derivatives, cyanurine, carbon, or iron.

6. There was complete disagreement regarding the following etiologic hypotheses: (*a*) Color arose from sebaceous glands. (*b*) Color derived from eccrine sweat gland. (*c*) Color came from pigmentary system of eye. (*d*) Color was due to carbon or dirt from air. (*e*) Color of unknown origin.

7. Nomenclature reflected varying views on etiology: (*a*) blackness of skin. (*b*) cyanopathia cutanea, (*c*) blepharomelaena, blepharocyanosie, (*d*) stearrhea nigricans, flavescens, *noire*, (*e*) melenastearrhea, (*f*) chromidrose or chromidrosis, (*g*) *chromocrinie partielle et cutanée*, and (*h*) cyanidrosis.

8. There was no satisfactory local or systemic treatment.

There has been no comparable period of intensive study since the era of 1850 to 1865. In fact, case reports on this condition have gradually diminished in number. Nevertheless, the literature and knowledge concerning chromidrosis has grown. By 1881 there were 44 cases of chromidrosis. In that year, Thomas Fox stressed the fact that heat, as well as emotion, might produce the secretion. He felt the pigment was in the sweat and not in sebum, and he claimed it was an indigo type of pigment, since these patients had an increase of indican in the urine and the pigment gave a purple color upon the addition of hot sulfuric acid. He also discussed the possibility of a bacterial genesis, which had been observed by Key.

By 1884 it was well established that colored sweat in the axilla could be due to pigments produced by bacteria. Among others, Babes had clearly described red sweat appearing in the axilla as a direct effect of the growth of chromogenic bacteria on the skin and hair. Babes showed on the basis of chemical and spectroscopic data that the red pigment found in the sweat was identical with that produced by the bacteria.

In 1884, the master of chromidrosis, de Méricourt, published a valedictory report entitled "Chromidrose rose." In this he described the first case of red chromidrosis he had seen in 30 years.

In 1888, Weber, in a study of the comparative physiology of mammals, concluded that all the known colored skin secretions in mammals arose from tubular glands. His studies included the red sweat of hippopotami and kangaroos, the blue sweat of the antelopes, and the black sweat of gazelles.

Heidingsfeld, in 1902, observed no abnormal histopathological findings except for pigment granules in the keratin.

Articles continued to appear on the role of bacteria in the production of colored sweat. In 1904, Trommsdorff reviewed this subject and related trichomycosis axillaris to red and yellow sweat. He believed blue sweat did not have a bacterial origin.

In 1908, Blanchard made a careful study of black sweat, which was seen in a boy aged 13. This melanhidrosis was localized to the eyelids and alae nasi. Microscopic examination of the coloring matter revealed fine shiny-black amorphous granules. The skin was observed with a binocular lens during secretion. The clear, colorless sweat which initially appeared became brown and later intensely black after drying. He felt that the sweat had formed an insoluble black pigment in the presence of air. The pigment was insoluble in fat solvents. Addition of sulfuric acid turned the pigment to a brown color. He concluded it was not melanin.

In 1930, Greig made the interesting observation that colostrum, milk, and sweat may each be similarly pigmented. Yellow, blue, or green milk has been noted by various observers.

In 1934, Pozzo reported a case of red axillary chromidrosis following injections of quinine iodobismuth. The patient did not have trichomycosis, and it was Pozzo's feeling that the colored drug was being excreted in apocrine sweat. The apocrine glands were incriminated because of the localization of the process.

Finally, in 1939, Samberger reported a case of red chromidrosis localized to the perianal area. The unique localization suggested to him that the process was due to an abnormality of the apocrine glands. He postulated a "nevoid" function of these glands in certain patients, with the consequent production of pigment.

Our interest in chromidrosis arose in the spring of 1949, when Dr. Lawrence Katzenstein, of Wilmington, Del., referred a young woman who had suffered with black sweating of the face for 10 years. Although initial studies suggested the possibility that the colored material was of apocrine-sweat-gland origin, it was not possible to confirm this until the basic physiology and pharmacology of the normal apocrine sweat gland had been determined. A short preliminary report of our later studies appeared in 1952. As the following account of our observations will disclose, it has been proved that true localized chromidrosis is an abnormality of the apocrine sweat gland.

CLINICAL AND EXPERIMENTAL FINDINGS

CLINICAL CASE REPORT.—*Chromidrosis of Face.*—This patient was a 29-year-old white unmarried woman in good health. She first noted what she described as "black sweat" on her cheeks at the age of 19. This dark fluid would appear at times of excitement, tension, or overheating, and was immediately preceded by an aura of warmth in the skin of the involved areas. The fluid dried to form a very dark flake or scale which was adherent to the skin. The process was worse in the summer and showed short unexplained remissions from time to time. Its appearance or severity showed no relationship to such factors as diet, menses, or general health. However, her menarche was at the age of 15, and a six-month period of amenorrhea preceded the onset of the chromidrosis. Sweating elsewhere was normal. The patient had always been in good health. There was no family evidence of any sweat abnormality. Alarm over the potential serious import of "black sweat" prompted the patient to seek the help of many physicians, and a wide

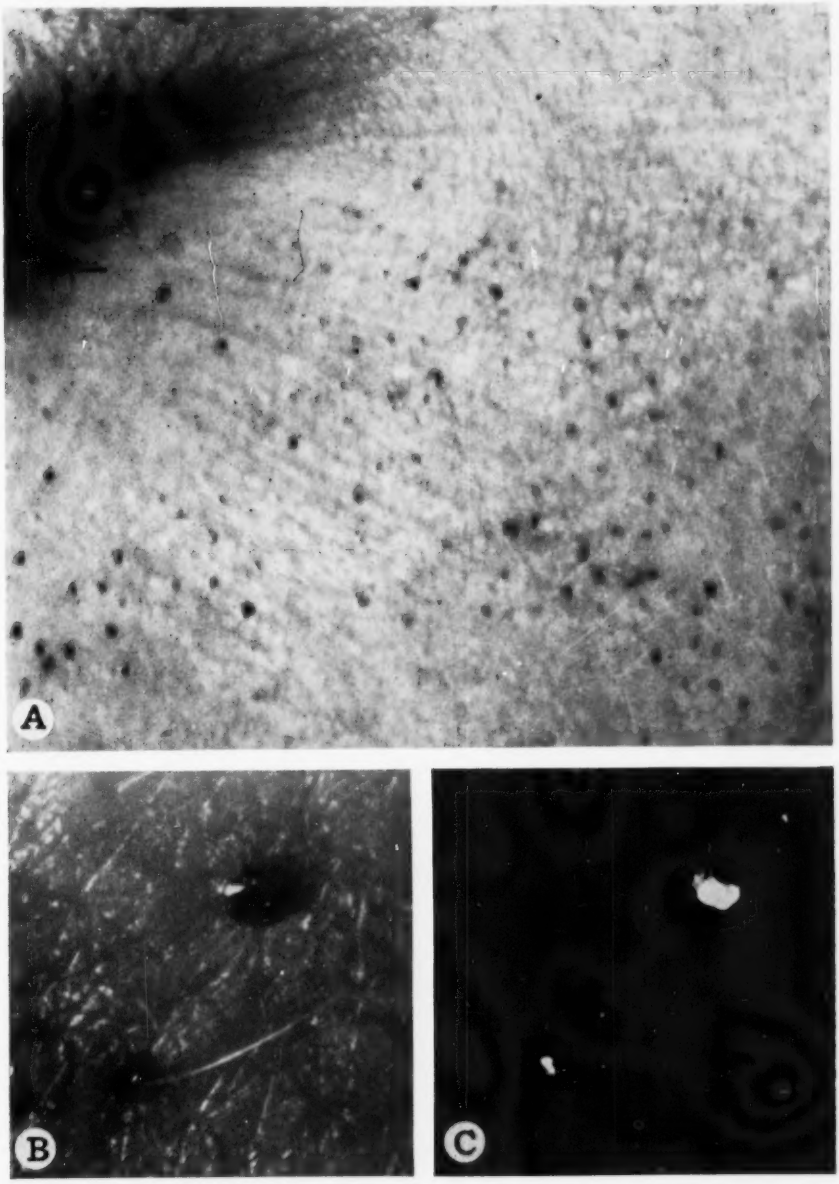

Fig. 2.—*A*, chromidrosis of the face. This is a photograph of the left cheek of our patient with chromidrosis of the face. This 29-year-old white woman produced varicolored sweat after emotional or thermal stimulation. Epinephrine also prompted this response, while cholinergic compounds did not. *B*, chromidrotic sweat. A close-up view of the colored sweat of the patient shown in *A*. Note the glistening, glue-like appearance of the dried secretion and its location at the orifice of the hair follicle. *C*, autofluorescence of colored sweat. Fluorescence of flakes of dried green-and yellow-colored secretion from the patient shown in *A*. Photograph was made with Wood light illumination of this secretion.

Fig. 3.—Microscopic view of apocrine gland found on face. Aberrant chromidrotic apocrine-sweat gland of patient shown in Figure 2*A*. Hematoxylin and eosin stain of biopsy from cheek showing apocrine gland in lower corium; × 250.

spectrum of topical therapy had been employed, to no avail. In addition, all cosmetics had been completely avoided for two years, without effect. A general physical examination revealed no abnormalities. Her skin was normal except for a few pitted acne scars on the face.

After five to ten minutes in a thermal chamber tiny black-and-brown puncta and droplets appeared on both cheeks. Before drying, the droplets could be wiped away readily. However, if undisturbed and in the absence of eccrine sweat, they dried rapidly, forming an adherent shiny-black, grayish-black, blue-black, or brown flaky material (Fig. *2B*). Many of these appeared to be in the sebaceous orifices. At ordinary room temperature an injection of 0.10 cc. of 1 : 1,000 epinephrine solution (commercial) in the left cheek produced about 25 droplets. Many of these were black, but some were white, blue, and green. An injection of 0.1 cc. of 1 : 100 pilocarpine nitrate solution in the right cheek gave a normal, colorless eccrine gland response. At a later date the local injection of 0.1 cc. of 1 : 1000 atropine sulfate solution had no effect and failed to prevent the appearance of colored sweat in response to epinephrine. Finally, it was found that the colored fluid could be expressed manually.

The lighter colored sweat showed a yellow fluorescence under Wood light (Fig. *2C*), whereas the black fluid and scale showed minimal or no fluorescence.

Study of apocrine sweating in the axilla revealed it to be normal and of the common white variety. The cerumen also showed the normal yellow-brown color.

Five-day patch tests with five of the patient's cosmetics were done. The readings were negative, and subsequent eccrine sweating in the area was colorless. Her urine was normal in color and nonfluorescent. It remained unchanged upon standing at room temperature.

Specimens of the colored fluid collected under sterile precautions revealed no bacterial growth. The dried scales were insoluble in water but disintegrated in ether and alcohol. However, the pigment itself did not appear to be truly soluble in these solvents.

Local treatment with ion exchange powders and hydrogen peroxide was without effect.

With local procaine (4%) anesthesia, a small biopsy was secured from the left cheek. On gross examination four small dark areas could be seen on routine sectioning and staining. These corresponded to the size and location of apocrine glands. In hematoxylin-and eosin-stained sections, these apocrine as well as eccrine glands could be seen (Fig. 3). The apocrine glands were small. The tubular secretory cells appeared more basophilic than normal and showed numerous yellow-brown granules of varying size and cellular location. Moreover, unstained histologic sections revealed these same yellow and brown pigment granules (Fig. 4*A*). Fluorescent microscopy demonstrated that these granules were autofluorescent (Fig. 5*A*). Myoepithelium could be found about the apocrine glands, with a phosphotungstic acid stain.

Special stains for lipofuscin (Schmorl, Hueck) revealed positively staining granular material in the apocrine tubular cell cytoplasm (Fig. 6*A*). The Hueck stain for melanin was negative. The Pearse stain for demonstrating acid-fast lipofuscins (ceroid) was weakly positive. Perls' ferricyanide stain for iron was negative (Table 2).

On the basis of these clinical, histologic, and physiologic observations, it was concluded that the patient had typical chromidrosis, and that the colored sweat was arising from aberrantly placed apocrine sweat glands.

Case Reports of Axillary Chromidrosis Discovered in Test Subjects.—Normally the axillae serve as the largest reservoir of apocrine glands. It was felt that subclinical chromidrosis should occur in this area if the hypothesis were true that all intrinsic localized chromidrosis is the result of abnormal function of the apocrine sweat gland. Accordingly, pure apocrine sweat, produced experimentally by the local injection of epinephrine (0.1 cc., 1 : 1,000), was studied in 100 male persons. Eleven cases were found in whom distinctly colored apocrine sweat appeared. In some only a few of the glands secreted colored sweat; in others the number of chromidrotic glands was large. In two instances the chromidrosis had been noted by the subjects, but in the others dilution with eccrine sweat had prevented recogni-

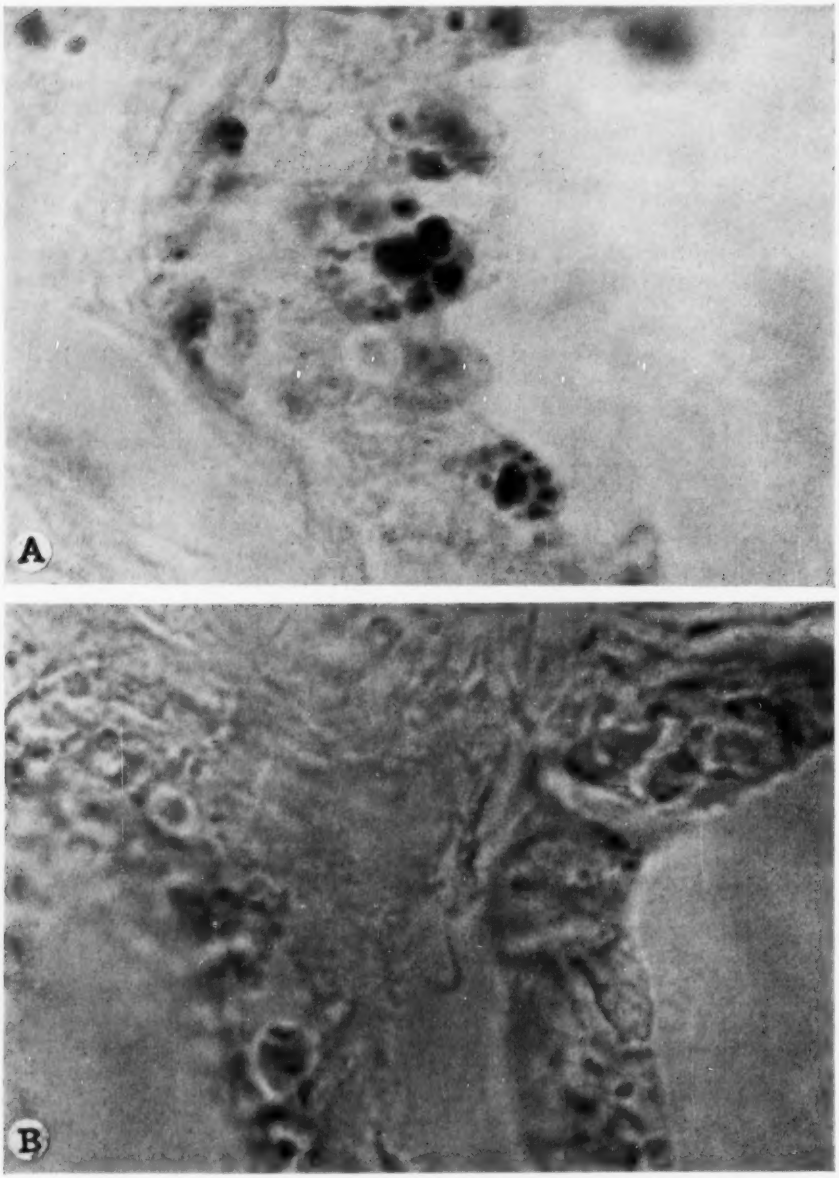

Fig. 4.—*A*, unstained apocrine granules in chromidrotic patient. This is a highly magnified (× 2,000) view of a portion of an apocrine-gland tubule from the cheek of the patient shown in Figure 2*A*. This specimen was unstained and revealed the presence of many variably-sized, yellow-brown pigment granules in the tubular cell. Note faint cell outlines; tubular lumen is in right half of picture. *B*, unstained apocrine granules in normal person. An unstained section at high magnification (× 2,000) from a nonchromidrotic control patient's axillary skin. This control biopsy is to be contrasted with that shown in *A*. Note the reduction in the number of pigmented granules.

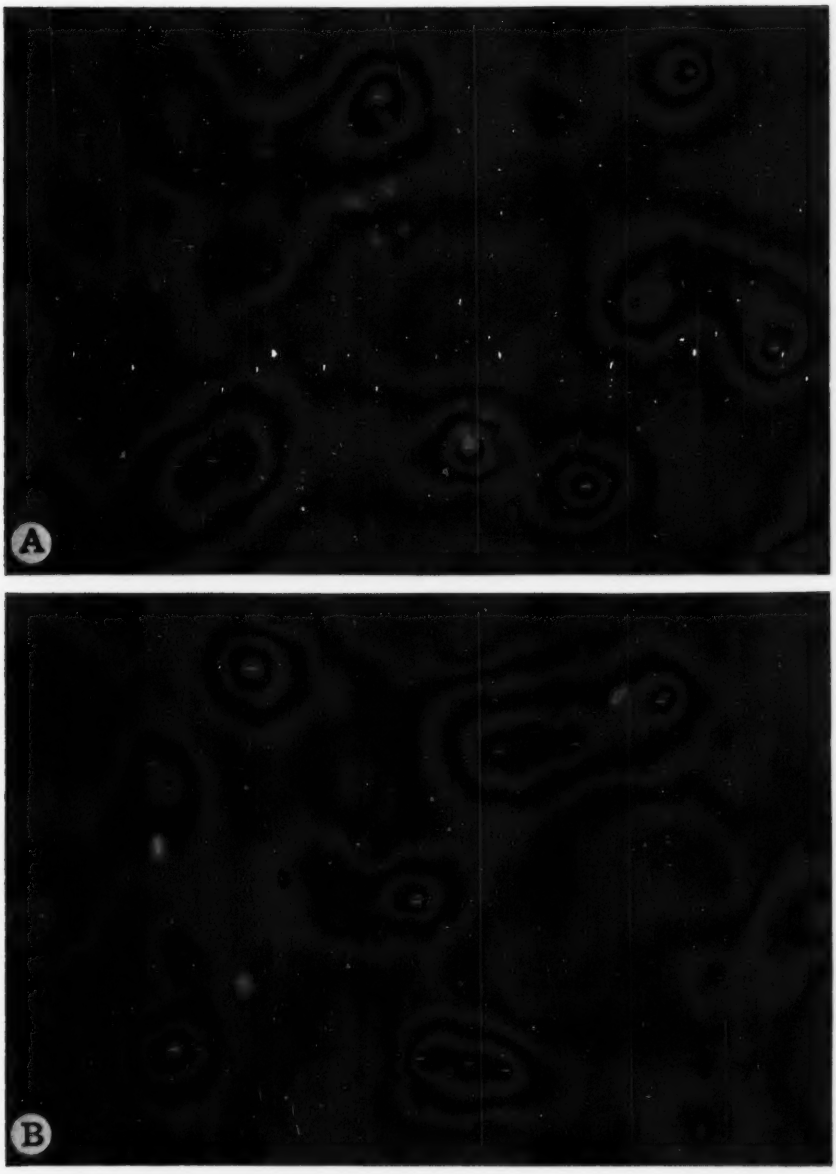

Fig. 5.—*A*, fluorescence of chromidrotic apocrine granules. This is a photomicrograph of the same granules seen in Figure 4*A*, as revealed by ultraviolet 4,000A. microscopy. Note that almost all these pigmented granules exhibit this autofluorescence. × 2,000. *B*, fluorescence of normal apocrine granules. This is a photomicrograph of the same microscopic field as is shown in Figure 4*B* using ultraviolet 4,000A. microscopy. Note that a smaller number of autofluorescent pigment granules are present in this control biopsy. × 2,000.

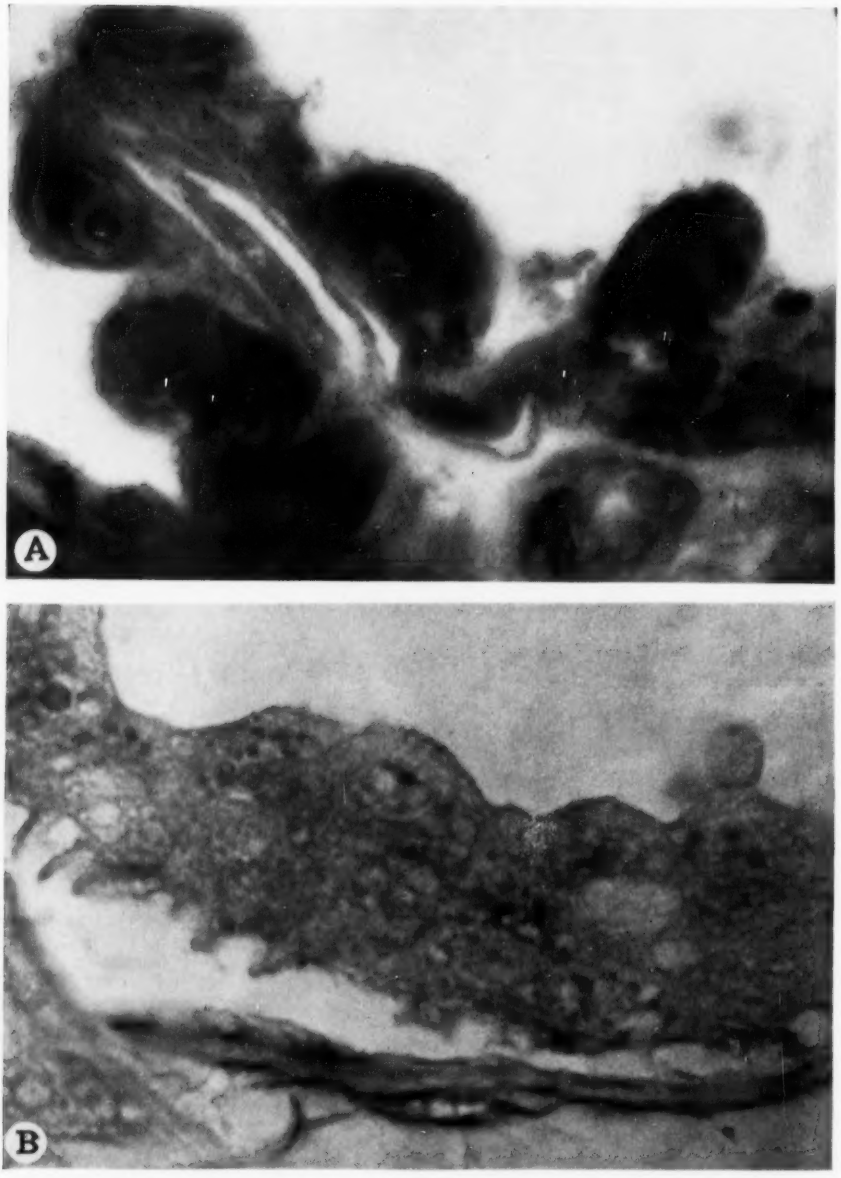

Fig. 6.—*A*, Schmorl reaction of chromidrotic apocrine gland. The numerous dark-staining granules seen in the apocrine tubular cell represent Schmorl-positive material (lipofuscin). × 2,000. *B*, Schmorl reaction of normal apocrine gland. The dark-staining granules seen in the apocrine tubular cell represent Schmorl positive material (lipofuscin). Note the diminished number of granules as compared with the chromidrotic gland (Fig. 6*A*); × 2,000.

tion. All these 11 men served as experimental subjects in further studies of the phenomenon of chromidrosis. For simplicity, the cases will be tabulated, and general discussion will be made of group findings.

General Clinical Findings.—In each instance the discrete colored droplets appeared within 20 seconds to three minutes after the injection of epinephrine. They appeared only in the blanched areas and usually at follicular orifices. They could be made to appear by mechanical stimulation of the skin, such as by stroking. In a previous paper this stimulation has been shown to cause contraction of the myoepithelium of the apocrine gland, with consequent expulsion of the contents. "Milking" the apocrine gland by simple sliding pressure on a fold of axillary skin was also effective in producing the colored fluid. This represents a partial mechanical expression of the apocrine gland contents.

TABLE 1.—*Axillary Chromidrosis Observed in 100 Male Test Subjects*

Color of Apocrine Sweat	Case No.	Age	Comment
Yellow	1	38	Heavy, profuse
	2	40	Numerous bright yellow droplets
	3	20	Occasional bright yellow droplets
	4	38	Occasional bright yellow droplets
Blue	5	19	Numerous single blue droplets
	6	20	Occasional blue droplets
Yellow, green, blue	7	37	Shirt armpit stained yellow; patient had "apocrine hyperidrosis" of yellow color with multiple blue or green droplets
	8	30	Shirt armpit stained yellow; patient had "apocrine hyperidrosis" of yellow color with multiple blue or green droplets
	9	25	Isolated chromidrotic droplets
	10	32	Isolated chromidrotic droplets
Yellow, green, blue, black	11	29	Predominantly white, but isolated droplets of various colors

Heat and local injection of pilocarpine (1 : 1,000) and acetylcholine (1 : 10,000) were ineffective in producing the colored material but did promote the flow of normal colorless eccrine sweat.

An interesting finding was the observation that, although an initial dose of epinephrine was effective in producing colored sweat, subsequent injections within the next 24 hours were without visible effect. However, after a rest period of approximately 24 hours, epinephrine did produce colorless or white sweat at exactly the same follicle or orifice. To produce the colored sweat required a rest period of a week or, in some instances, several weeks. Thus it was observed that there was a refractory period for chromidrosis from a unit gland which distinctly exceeded that known to exist for white apocrine sweat. If the gland was incompletely emptied as a result of neural stimulation, no refractory period was observed.

It should be pointed out that in some instances apocrine sweat appeared colorless initially but after a period of evaporation color appeared. Very frequently in all

100 of the test persons the white sweat became yellow on standing and dried to form a yellow varnish-like cap, if not diluted with eccrine sweat. As a general rule, it was found that the darker the color of the fluid, the smaller the quantity.

Direct examination of the apocrine glands in situ (stereoscopic microscope 30 ×), following deep axillary incision revealed a color of the tubules comparable to that seen in the sweat. Normal glands were white, whereas those secreting yellow fluid were yellow, and the ones from which blue and green sweat appeared were bluish-black in color. Grossly, the other appendages and the dermis and subcutaneous tissues were normal in color.

Observations on Colored Sweat.—Colored sweat had exactly the same physical characteristics as apocrine sweat. It was quite unlike eccrine sweat. It ranged from the thick semisolid variety to a thin faintly turbid fluid. Its volume was very small, a single droplet approximately 0.001 cc. Observation of the sweat under Wood light (3,660 A.) revealed that yellow, green, and blue sweat had a common yellow fluorescence in an ascending intensity. Thus, blue sweat had an intensely bright yellow fluorescence, whereas yellow sweat gave a moderate yellow fluorescence.

TABLE 2.—*Histochemical Studies of Pigmented Granules of Normal and Chromidrotic Apocrine Sweat Glands (Formaldehyde-Fixed Specimens)*

	Subject Number	Biopsy Site	Number of Granules	Fluorescence	Lipofuscin Stain (Schmorl Reaction, 34)	Lipofuscin Stain (Hueck Stain, 34)	Cerold (Pearse, 34)	Iron (Perls, 35)
Chromidrotic	6	Face	++++	Yellow	++++	++++	+	0
	7	Axilla	++++	Yellow	++++	++++	0	+
	8	Axilla	+++	Yellow	+++	+++	0	++
	11	Axilla	++++	Yellow	++++	++++	±	++
Normal	1	Axilla	+	Yellow	+	+	0	++
	2	Axilla	+	Yellow	+	+	0	+

Noteworthy is the fact that black sweat was relatively nonfluorescent. Control studies showed that normal white apocrine sweat generally fluoresced faintly under the Wood light but frequently had some yellow fluorescence. The fluorescence of dried yellow sweat was perfectly stable for periods longer than a year.

Paper chromatography revealed that the fluorochrome and the pigment had the same migratory pattern. The question of solubility of the pigment was explored. Dried colored sweat was insoluble in water but did disintegrate in 70% ethyl alcohol. Although initially it was felt the pigment dissolved, observation under the microscope revealed that the pigment particles remained discrete and did not go into solution. Furthermore, the pigments proved to be insoluble in carbon disulfide, chloroform, carbon tetrachloride, and pyridine.

The initial pH of the colored sweat was approximately 6.0. Alterations of the pH of blue sweat had no effect on the color.

Upon the addition of a crystal of the strong reducing agent sodium hydrosulfite, blue sweat became decolorized.

Normal white apocrine sweat became yellow-brown on standing for several weeks. A crude nonspecific test for carotenoids was positive. Addition of sulfuric acid to a drop of yellow sweat on filter paper produced delicate strands of reddish material, later becoming a diffuse violet. The Carr-Price antimony reaction for vitamin A was negative.

Bacterial cultures of specimens of colored sweat taken under sterile conditions were negative.

Histologic Observations.—The histologic data obtained from biopsies of three of these patients can be summarized in tabular form (Table 2).

COMMENT

Two major questions have always confronted the investigator of the problem of localized chromidrosis:

1. What is the source of this colored secretion?
2. What is the chemical nature of the colored material?

In answering the first question it is essential to study the possibility of external causation, such as artefact, obscure chemical contactants, and the chromogenic microflora. After such causes have been eliminated, there still remains an "essential" intrinsic chromidrosis. It is our finding that such a type of true localized chromidrosis arises on the basis of an abnormality in apocrine sweat-gland function. The evidence we have accumulated for this hypothesis is of four categories:

1. *Anatomic and Physical.*—True chromidrosis occurs in skin in which grossly pigmented apocrine sweat glands are found. Chromidrotic sweat and colored secretions, formerly felt to arise from the sebaceous gland, are physically identical with the range of characteristics seen in apocrine sweat. The secretion is turbid, generally appears at a hair-follicle orifice, and dries to form a glistening glue-like mass.

2. *Histologic.*—Pigmented apocrine sweat glands have been found in four cases of chromidrosis. The pigment is found in the secretory cells of the apocrine tubule. In the one case studied in which the localized chromidrosis occurred on the face, aberrantly placed apocrine glands were found. It is to be stressed that aberrant or heterotopic apocrine glands have been found by a number of other observers.

3. *Physiologic.*—The chromidrotic material always appears in response to measures and drugs which specifically stimulate apocrine sweat glands. The only exception to this occurred in a patient in whom high environmental temperature served as a stimulus. This probably represented an abnormal adrenergic stimulus, since cholinergic drugs were ineffective.

4. *Comparative Physiologic.*—In several animals, colored sweating occurs. Reference is made to the hippopotamus, which secretes a reddish-brown slimy material onto its skin. Other examples of localized chromidrosis are seen in the elephant, antelope, and gazelle. In many instances, an apocrine-like sweat gland is responsible for the colored secretion.

It is noteworthy that the apocrine sweat gland in the axilla is a prototype apocrine gland in man. In this respect the mammary gland, a highly specialized apocrine gland, occasionally produces a colored secretion.

In addition, it is important to examine another of the modified apocrine glands of the human body, namely the ceruminous glands of the ear canal. The color of the waxy secretion of these apocrine glands shows racial variation. In the Oriental, this secretion is usually white.* In contrast, the Occidental normally produces yellow or brown ear wax. Thus it is apparent that the latter group actually has

* Reference 39 and from personal observation.

localized chromidrosis of the ear canal. This is a normal phenomenon and as such is not recognized as chromidrosis until a study of these racial differences makes it evident.

To turn to the problem of the nature of the colored material in apocrine sweat, it has been necessary to employ a histochemical approach. The minuteness of the specimens obtainable precludes the regular employment of ultramicrochemical and microspectroscopic methods.

From the cytologic standpoint the normal apocrine secretory cell is remarkable for the presence of pigmented granules. In the unstained specimen these may be seen as variably sized round or oval and, at times, irregular granules. They may be found anywhere in the cytoplasm, but they are found to be most abundant supranuclearly. In color they range from the large round golden-yellow variety to the smaller brown to black types (Fig. 4*B*). Many of the cells may contain relatively few or none. The majority of these granules show a yellow autofluorescence (Fig. 5*B*). Moreover, they possess the ability to reduce ferricyanide (Schmorl reaction) (Fig. 6*B*). These granules may show a positive test for iron. The granules are not removed by aqueous or hydrocarbon solvents.

In the secretory cells of the chromidrotic apocrine gland there is a marked increase in the number of pigmented granules (Fig. 4*A*). There is also a striking increase in the number of cells containing these granules. Histochemically, the granules are identical with those seen normally (Figs. 5*A* and 6*A*). It must be stressed that the fundamental difference between the normal and chromidrotic apocrine gland is a quantitative one.

With this knowledge in mind, a survey was made of the various biological pigment groups. Pearse has reviewed the problem and has arranged pigments into three main divisions: (1) tyrosine group, which includes melanin, chromaffin, and argentaffin granules; (2) haem group (porphyrins), which includes hemoglobin and its derivatives, and (3) lipopigments, which includes the lipofuscins, ceroid, and the carotenoids.

A comparison of the histochemical properties of these groups with those of the apocrine granules leads us to conclude that the pigment granules of the apocrine gland are lipofuscins.

We have eliminated the tyrosine group because its members are nonfluorescent. In addition, melanin stains were negative. The porphyrin group was excluded on the basis of differential solubilities and fluorescence.

In the lipopigment group we were impressed by the fact that the lipofuscins possessed many of the characteristic seen in the pigment granules of the apocrine gland. Pearse has clearly described the properties of this hitherto diffuse group of pigments. These lipofuscins have also been known as "wear-and-tear pigments" (*abnützungs pigment*), brown atrophy chromolipoids, cytolipochromes, hemofuscin, lipochrome, and ceroid. They are derived from lipid and lipoprotein sources.

Pearse views the histogenesis of lipofuscins in a broad inclusive manner. He depicts a spectrum of progressively oxidized compounds. The lipid precursors, at the one extreme, possess all the chemical and physical characteristics of fats. Gradually, by a process of oxidation, the following changes arise:

1. The color increases and progressively darkens.
2. Basophilia develops and increases in intensity.

3. The solubility in fat solvents diminishes. Sudanophilia parallels this change.

4. Fluorescence is prominent in the intermediate stages but is absent in the compounds less and greater degrees of oxidation. Very light-colored or very dark-colored lipofuscins are nonfluorescent.

5. There is a progressive increase in the number of reducing groups. This is revealed by the Schmorl reaction, which has been used as a test for lipofuscins.

Ceroid, commonly viewed as a unique acid-fast pigment, is considered by Pearse as an intermediate stage between auto-oxidizing lipid and lipofuscin.

The pigment granules of both the normal and the chromidrotic apocrine gland show the same spectrum of properties as seen in the lipofuscin group. They vary in color, basophilia, sudanophilia, solubility, fluorescence, and number of reducing groups (Table 2).

It is our view that these pigment granules are responsible for the colors seen in the apocrine sweat. Thus, yellow sweat, the commonest variety, is due to the presence of a large number of lipofuscin granules in a lower stage of oxidation. Black sweat contains a large number of highly oxidized lipofuscin granules. Intermediate colors, green and blue, reflect the presence of intermediate lipofuscins. It is important to note that the fluorescence of these different-colored secretions corresponds with the fluorescent pattern of the lipofuscin group. Yellow, green, and blue sweat all showed a yellow fluorescence of increasing intensity. Black sweat was relatively nonfluorescent.

It is interesting to note that ceroid, an intermediate stage between lipids and lipofuscins, is not present in appreciable quantities in the normal gland. However, it was found in small amounts in several of the chromidrotic glands. This is in accord with the finding of massive amounts of lipofuscins in such cells.

Correlation should be made with the histochemistry of the apocrine glands of the ear canal in relationship to color. Montagna, Nobach, and Zak, in a detailed account of the histochemistry of the ceruminous glands in man, found pigment granules to be scarce in an Oriental subject. In contrast, they observed abundant pigment granules in all Caucasians. This difference in granule content parallels the differences seen in the color of ear wax of the Oriental and Occidental groups. The reduction in granule content results in a white or colorless secretion.

A study of Montagna's data concerning the properties of the pigment granules of the wax glands leads us to conclude that these granules are also lipofuscins. Sections from the ear canal of people producing yellow-brown ear wax show apocrine glands with pigment granules in amounts comparable to those seen in our chromidrotic patients.

We have no evidence that carotenoids (carotenes, xanthophylls, vitamin A) are the primary pigmentary substances in colored sweat. However, we have demonstrated trace amounts of them in apocrine sweat by means of a spot test with sulfuric acid.

We cannot subscribe to the commonly held view that indican or indigo blue is responsible for the color in blue sweat, since, again, these compounds are nonfluorescent and, furthermore, their presence would not explain some of the other colors seen.

To recapitulate, the differential diagnosis of tissue pigments is, fortunately, a difficult one. There are no specific histochemical tests available at present. However, on the basis of our current knowledge, we should like to suggest that the lipo-

fuscin group of pigment is responsible for the color in colored apocrine sweat. We feel that the varying color observed in chromidrosis reflects varying concentrations and states of oxidation of lipofuscin. It is our impression that this lipofuscin group of pigments is present in all apocrine sweat and that it is only after a critical concentration or an abnormal state of oxidation is reached that visible color changes are produced. It should be noted in this regard that white apocrine sweat commonly dries to leave a yellow residue. We interpret this as a concentration of the yellow pigment normally masked by the white apocrine sweat. Furthermore, although normal white apocrine sweat usually has a faint whitish fluorescence, many specimens show a distinct yellow fluoresence. This yellow fluoresence may be attributed to the presence of the yellow lipofuscin which can be detected more readily in Wood light than in visible light.

It should be pointed out that the subjects described in Table 1 had relatively large numbers of chromidrotic glands. Actually, a few droplets of yellow sweat may be produced in about a third of the subjects we have studied.

All evidence points to the fact that the pigment is produced intracellularly. Significant color changes cannot be induced by allowing normal or colored sweat to stand at room temperature for several days. Furthermore, experiments have been conducted in which apocrine-sweat retention was produced. This apocrine sweat was retained within ductal cysts for periods of three weeks. At the end of this time, the apocrine sweat was white.

It must be stressed that single specific glands show this property of producing lipofuscin in quantities or in oxidative states sufficiently high to produce chromidrosis. If these glands are completely emptied by the injection of epinephrine, the return of colored sweat is delayed. Initially, white, normal-appearing sweat is produced by these glands, and it is only after a period of many days that the color returns. We would attribute this to a period necessary for synthesis of the more highly oxidized lipofuscins.

We have been impressed by the fact that the intensity of the color of the apocrine sweat varies inversely with the quantity produced. In the two persons in whom black sweat was observed, the quantity produced was minimal, and drying occurred within a matter of seconds. This was correlated with the presence of small apocrine glands.

There is no knowledge of the role of iron in the apocrine gland, but it may be that it enters into the oxidative processes responsible for lipofuscin. In any event, iron does not appear to be increased in amount in chromidrotic glands or in colored sweat.

Many of the reports in the literature describe red sweat of the axilla. This has always been associated with bacterial chromogens. We have no evidence that the apocrine gland can produce a red pigment.

Ordinary localized chromidrosis of apocrine origin is a normal condition and, as seen in the axilla, for instance, requires no treatment. However, the aberrant placement of these chromidrotic glands may give rise to a clinical problem. The patient should be reassured concerning the significance of this colored secretion. If a cosmetic problem exists, e. g., in chromidrosis of the face, treatment is difficult. Topical measures are limited in their effectiveness, usually serving only to aid in removal of the dried secretion. Systemic medication, such as use of sympatholytic

compounds, has not been satisfactory. Destructive measures are usually impractical in view of the relatively large number of glands involved.

We are studying the effects of hormones, x-rays, and dietary restriction of carotenoids on chromidrosis in the hope that alterations of the lipofuscin metabolism may be achieved.

SUMMARY AND CONCLUSIONS

On the basis of observations on 12 persons with chromidrosis the following conclusions has been reached:

1. Intrinsic localized chromidrosis is an abnormality in which colored apocrine sweat is produced. The colors seen are yellow, green, blue, brown, and black. The affected apocrine sweat gland grossly presents a color closely resembling that of the sweat. The number of glands producing colored sweat is variable. Localized chromidrosis may occur anywhere on the body, but its occurrence always indicates the presence of underlying apocrine glands, either normally or aberrantly placed.

2. The colored apocrine sweat is discharged from the gland in response to emotional stimuli, epinephrine, or mechanical stimulation of the myoepithelium of the gland. A single gland, after complete emptying, resynthesizes apocrine sweat, which at first is colorless or white. After one week of rest the gland may again produce colored sweat. The quantity of sweat is usually inversely proportional to the intensity of the color.

3. Direct visualization of single apocrine-gland function is requisite for the study of unit-gland chromidrosis. Contamination with normal white apocrine sweat or eccrine sweat may readily mask single droplets of colored sweat.

4. Yellow, blue, and green sweat show a common yellow fluorescence when viewed under Wood light. Black sweat shows little or no fluorescence. The dried colored apocrine sweat may be partially dissolved in fat solvents, but the pigment per se is insoluble.

5. Histologic and histochemical study of normal and chromidrotic apocrine glands reveals in both types the presence of pigmented granules possessing the properties of the lipofuscin pigment group. The difference lies solely in the number of granules present. It is possible histologically to make the diagnosis of apocrine chromidrosis solely on the basis of the appearance of numerous pigmented granules in the secretory cells. The normal gland exhibits relatively few of these granules.

6. On the basis of the present studies it is felt that the color of apocrine sweat in chromidrosis is due to varying amounts of lipofuscin (cytolipochrome) in different states of oxidation. The higher states of oxidation result in the darker colors.

7. Analogy is drawn to the colored apocrine secretions which may occur in the mammary gland, the wax glands of the ear canal, and in mammalia other than man.

8. Direct observation of single glands has shown that from the unit-gland standpoint apocrine chromidrosis is not rare. However, this chromidrosis rarely manifests itself clinically, since apocrine sweat is produced in such small amounts as to lose its identity and color by dilution with eccrine sweat.

Miss Sondra Golomb, Miss Anna Nichols, Mrs. Verna Stein, and Mr. Walter N. Davis gave assistance in various aspects of this study. Mr. Edward Glifort supplied the photographic illustrations.

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ABSTRACT OF DISCUSSION

DR. WALTER C. LOBITZ, JR., Hanover, N. H.: I can only speak with great enthusiasm and praise for the work on the apocrine gland that is being carried out by Dr. Shelley and Dr. Hurley. As is always the case, the discusser has an opportunity to study the detailed manuscript of such a report that of necessity is presented in abbreviated form. Dr. Shelley's manuscript itself deserves special praise, since it leads one in an exciting and orderly fashion through the entire history of chromidrosis, in addition to contributing new knowledge to the subject. As such, then, it answers many questions that might arise at a time like this, when only the abbreviated presentation is available.

This subject of chromidrosis is a fascinating one. Colored sweat, as seen by the clinician, may be generalized or localized. These two major groups can then each be subdivided into (1) true chromidrosis (or intrinsic chromidrosis), in which eccrine or apocrine sweat is truly colored, or (2) false or pseudochromidrosis, in which there is an extrinsic or external source for the pigment once the sweat has been secreted. These studies by Drs. Shelley and Hurley are bringing light to the understanding of one particular type of localized, true (intrinsic) chromidrosis—the chromidrosis of unit apocrine-gland origin.

On several occasions this past year I was fortunate in being able to visit the laboratory of Drs. Shelley and Hurley. They were kind enough to show me, firsthand, many aspects of this work on apocrine gland physiology, thus explaining my lack of skepticism as well as my enthusiasm.

There is no question that certain individual apocrine-gland units will secrete a colored material. The next questions are, of course, what is the cytological origin of the pigment within the apocrine secretory cell, and what is the chemical nature of the coloring material? The studies to date of Drs. Shelley and Hurley indicate that chemically the coloring material is in the class of lipopigments of the lipofuscin type and that the colored material lies within the cytoplasm of the cell as a pigment granule.

In this regard, I should like to present four questions to Dr. Shelley. The histochemical studies on human skin that I am doing with Dr. Montagna have identified three chemical types of cytoplasmic granules in the apocrine secretory cell: a small pigmented granule, a large pigmented granule, and a nonpigmented granule (which will vary in size). There are histochemical differences between the small pigmented granules and the large pigmented granules and also between the pigmented and nonpigmented granules.

The first question: Am I correct in assuming that the large pigmented cytoplasmic granules are the ones responsible for apocrine sweat pigment?

The second question: When Dr. Montagna and his associates studied the ceruminous type of apocrine gland in the external auditory meatus of man (Montagna, W.; Noback, C. R., and Zak, F. G.: Pigment, Lipids, and Other Substances in the Glands of the External Auditory Meatus of Man, *Am. J. Anat.* **83**:409-431, 1948) they demonstrated that the yellow pigment is insoluble in water and sudanophilic when it lies within these apocrine (ceruminous) cells. However, when the pigment is in the residual cerumen, free in the ear canal, it is soluble in water and is not sudanophilic. Does this apocrine pigment of chromidrosis possess similar chemical solubility differences depending on whether it lies intracellularly or extracellularly?

The third question: Dr. Holyoke and I (Histologic Variations of Human Eccrine Sweat Glands, *J. Invest. Dermat.* **18**:147, 1952) found a lipochrome pigment in the cytoplasm of eccrine sweat gland secretory cells and correlated this with the age of the patient. Is any such correlation possible with the yellow pigment of the apocrine cell?

The last question: Is it possible that the specific color of the pigment under discussion might reflect a genetic or racial background of a given person?

DR. MARION B. SULZBERGER, New York: I, too, want to thank and compliment Dr. Shelley and Dr. Hurley for this very interesting and very fascinating presentation. I am looking forward to reading the complete paper when it appears.

I should like to point out just one small facet of the many things that Dr. Shelley's paper brings to one's mind—that is, the question of the word "sweating," the term "sweating" itself. Dr. Herrmann and I, who have just been engaged in writing a summarizing monograph, a short monograph on the disturbances of human sweating, found that the mere term "sweating" is now

really no longer adequate to express the many phenomena concerned. As you see from Dr. Shelley's presentation, the phenomena of the secretion or formation of sweat must be separated from the phenomenon of the outpouring of the sweat or its expulsion to the surface of the skin. The secretion of the sweat, whether white or colored, showed a lag; the coloring of the sweat showed a greater lag, up to a week, than the formation of the white material. Well, this is only one part of sweating, the secretory part—what the acini of the glands do, whether they be apocrine or eccrine, in the formation of what we call sweat.

A second part of sweating is getting the secreted sweat onto the skin surface, and that may be a function of different structures—in this case of the myoepithelium. In writing and talking we are constantly faced with the quandary of how to express these two different parts of what is commonly called sweating—the formation and secretion by the acini on the one hand and on the other hand the pouring out or moving out of the sweat to the skin surface. This dilemma is particularly acute when the ducts are obstructed and the acini are still functioning.

So Dr. Herrmann and I have been constrained to use the terms "pouring out of the sweat onto the surface" or "delivery of sweat," instead of simply saying "sweating" to describe what we see when the droplets appear at the skin surface or when the surface got wet.

That distinction is, I think, of more than semantic interest, because there is not only the possibility but also the strong probability or even the fact that one of these functions, secretion, may be under the influence of a certain set of nerves, let us say, cholingeric, whereas the outpouring may be under the influence of another set of nerves, say, the adrenergic nerves, as in the case of the contracture of the myoepithelium, as I tried to point out in a recent symposium on sweating, in which Dr. Shelley also participated (A. M.A. Arch. Dermat. & Syph. **66**:162-179 [Aug.] 1952). Of course, you will all recognize how far-reaching this distinction is in neurology, in the studies of nerve damage and nerve recovery, as well as in the studies of the effects of drugs and emotions upon sweating, to name but a few examples. In the future, one will have to separate sharply—in speaking, in writing, and in thinking—the function of secretion and the things which control that and the function of the pouring out or delivery of the material called sweat and the factors which control that.

What is true here in the case of sweat is probably true also in the case of the sebaceous glands and sebum. The formation of sebum by the sebaceous glands is one function, and the other function is the pouring out and spread of that sebum over the skin surface. It is this latter set of phenomena in which Dr. Herrmann and his co-workers and I have been particularly interested, and in recent years we have made some progress in showing the relationship between sweat and the emulsification of sebum and the pouring out of sebum onto the skin surface—as contrasted with the secretion of sebum. We think that many authors who today believe they see a nervous and emotional effect upon the secretion of sebum are actually not studying any nervous mechanisms with relation to the secretion of the sebum but are simply studying the effects of sweat and also of other factors upon getting sebum out of the sebaceous gland orifices and spreading it onto the skin surface.

I want to thank Dr. Shelley again. As I said, I congratulate him and know we are all looking forward to reading his excellent paper.

Dr. Joseph V. Klauder, Philadelphia: I am sure we all appreciate this excellent presentation. To my knowledge, it is one of the first pieces of documented evidence in explanation of that most curious phenomenon of colored sweating.

I have been particularly interested in this as one exotic cutaneous manifestation. As collateral reading in writing my paper, "Stigmatization" (Arch. Dermat. & Syph. **37**:650, 1938), I reviewed, in a measure, the literature on colored sweat. Some writers, for example, thought there may be a relation of colored sweat to the stigmatas, but I am sure that that is not the case, at least in some of the authentic stigmatists, as Therese Neumann, about whom I wrote.

There has been little recent literature on colored sweating. I think Dr. Shelley is to be congratulated that he had some subjects to study. I have been looking for years for such subjects. It appears that they were more commonly seen in the days of Charcot (about 1860 to 1880). If I remember correctly, the condition was regarded as a hysterical manifestation; perhaps this view was influenced by the Charcotian period. Again, if my memory serves me correctly, the phenomenon has been produced under hypnosis. I would be interested in knowing the emotional background of these patients and, too, if it is possible, I should like to hypnotize them to see if one could produce, by suggestion, a variety of colored sweat.

Dr. Shelley, too, may wish to correlate this phenomenon with what is called the blue edema of hysterics, of which I have been trying to find a subject. Apparently, it is a disappearing exotic lesion. Psychiatrists tell me that they have not seen blue edema in hysterics for some years. I have an intuition that there may be some relation between the two phenomena.

Dr. Shelley, too, I think, may be interested to know that chromidrosis is discussed in that remarkable book by that remarkable man, Gould (Gould, G. M. and Pyle, W. L.: Anomalies and Curiosities of Medicine, Philadelphia, W. B. Saunders Company, 1897). He was a Philadelphian —not that he was remarkable because he was a Philadelphian.

Dr. Stuart C. Way, San Francisco: A case recently seen presented a greenish-blue discoloration of the fingertips. These areas contain eccrine glands, and while there has been no time to carry out extensive studies, it was noted that the intensity of the pigmentation varied with the amount of indican in the urine. I should like to hear from Dr. Shelley as to his experience with regard to indican as a possible cause of pigmentation.

Dr. Fred D. Weidman, Philadelphia: To the pathologist, pigments are divided into three categories—the hematogenous, the hepatogenous, and the autochthonous (or metabolic). Doubtless, this particular pigment of sweat glands falls into the last group. As Dr. Shelley indicated, one name that has been applied to the lipofuscin pigments is "waste pigment," and their commonest expression is that in the "brown atrophy of the heart" of senile subjects as seen in sections from autopsy material and is put down as "lipofuscin." Certainly, it is the pigment of a wasted heart.

To cite an additional example, Montagna and Melaragno (Histology and Cytochemistry of Human Skin: III. Polymorphism and Chromotrophy of Mast Cells, *J. Invest. Dermat.* **20**:257-261, 1953) have reported recently concerning the varying staining qualities of mast-cell granules in the skin, and I have observed transitions of color into brown, also, like lipofuscin. This could be explained on grounds that the variation in the chemical composition of the granules depends upon the fact that they are waste products. The differences in affinity for toluidine blue would be referable simply to rearrangement of the molecular composition of the particular compound concerned at this or that stage of the degenerative (wasting) process. I regard the granules not as functionally specific but as degenerative.

Another waste substance which has received special attention lately is one which is known as ceroid and which has been studied especially in dogs. Errors of metabolism in the liver are accompanied by the formation of ceroid in it, and, in my laboratory, Dr. Louis Jaffe demonstrated it in the apocrine glands. The technique is simple, the ordinary acid-fast method stains the granules red. With this background as a help, I judge that the signs point to the likelihood that this pigment of the axillary and apocrine glands is in the nature of a waste substance and not a purposeful and useful secretory substance.

Another example of colored sweat is furnished in the case of the so-called bloody sweat of the hippopotamus. In very hot weather, beads of it appear which are so large that they can be seen from the front of the cage. Naturally, blood was the first explanation advanced for the color, but this was easily disproved. Another theory was stated and disproved, namely, that it was due to contamination of the sweat by micro-organisms, and it is true that the so-called "pink torulas" are commonplace saprophytes occurring between toes and elsewhere on man (incidentally, they may occupy the urinary bladder and color it so that the pink urine has been mistaken as evidence of hematuria). This bloody sweat of the hippopotamus is doubtless due to the same mechanism as in chromidrosis.

The outstanding item of interest to me in Dr. Shelley's presentation was that so many persons, 11, I think showed at least a trace of this pigmenting material in their sweat; in homely words, there is at least a little bit of chromidrosis in even the best of us.

Dr. Walter B. Shelley, Philadelphia: I want to thank all the discussers for their kind comments. I will try to answer some of the questions that were brought up.

In regard to Dr. Lobitz' question as to the size of the granules responsible for this colored sweat, we feel that probably all the granules, both the small and large pigmented granules, entered into the production of this color; at least, we are in no position to make any distinction, other than the fact that the larger granules are yellow and yellow-brown, so that they presumably would be in higher concentration in the yellow sweat, and that the smaller granules were darker in color and might be incriminated more in the darker colored sweats which we have observed.

We noticed that the solubility of these pigments did not change after the pigment was excreted from the cell; in other words, the chromogens are water-insoluble both in the cell and in the dried sweat. This is in contrast to findings of the studies that were done on cerumen that Dr. Lobitz mentioned.

As to the point about age, I think that is a very interesting problem, but we have no information to indicate whether or not the chromidrosis or pigment granules would be commoner in the older persons.

The last question Dr. Lobitz asked was about genetic or racial background. I think that is a very significant point. We do feel that the color in these glands may reflect a genetic or racial background. I should like to mention one example which does not bear directly on our work and yet is pertinent; that is, the fact that the apocrine-gland system in man is a broad one. It is not only responsible for the sweat produced in the axilla, around the anus, nipples, and so on, but it is also really the prototype gland for the ear-wax gland, that is, the ceruminous gland, and also the mammary gland.

In regard to the ear-wax gland, I should like to point out that Oriental persons, the Japanese and the Chinese, have white ear wax; in other words, their apocrine glands in the ear canal produce a colorless or white product, whereas we have yellow-brown ear wax; hence, in reality, all of us have localized chromidrosis in our ear canals.

In regard to Dr. Sulzberger's points, I heartily endorse his comments on the diffculties in nomenclature. We are constantly struggling with them. We have simply designated secretion as the process occurring in the cell and sweating as the appearance of the material on the surface of the skin, but that does not cover all the possibilities and probabilities that Dr. Sulzberger pointed out.

The same situation obtains in the physiology of the mammary gland. There, the physiologists are confronted with the secretion of milk, which remains in the mammary gland until it is let down and brought to the surface. In that case, there are three distinct processes occurring.

With respect to Dr. Klauder's comments, we do not feel that this apocrine gland is responsible for those cases of bloody sweat, and one reason for this view is the fact that we have never observed any red pigments. Perhaps they occur intrinsically, but we have not seen them. The red pigment which is seen in the axilla from time to time and may color the sweat there is a bacterial chromogen. All this is not proof, of course, but so far as I know true intrinsic chromidrosis of a red color has not been reported, and that thought goes down through the literature of the last century and a half. It was always felt that the red color was due to a bacterial contaminant producing chromogens on the surface.

As to the point about why chromidrosis is such a rarity today, I do not know. We have puzzled over that a great deal. As I say, we have seen only the one clinical case, the girl with the chromidrosis of the face, and it may be that there is a question of cleanliness entering into this, because the patient I showed you from 1845 showed the secretion which had accumulated over a period of five days. She was so overwhelmed by the appearance of this material on the skin that she never removed it. Today, our habits of washing frequently with soap probably rule that out.

I suspect that the chromidrosis in our patients could be induced by hypnotic suggestion, i. e., simply a routing of the stimulus down through the adrenergic portion of the sympathetic nervous system, so the material could be forced to the surface of the skin at any particular time.

Dr. Way has a very interesting patient, the one with the greenish-blue sweating at the fingertips, and I hope that he will do further studies. We ruled out indican as the causative agent in our patients on the basis that its chemical properties are incompatible with those of the pigment granules we have seen under the microscope. However, Dr. Way's findings are in agreement with the most popular of present-day theories as to the cause of localized chromidrosis, viz., indicanuria, with indican excretion in the sweat.

Dr. Weidman's final points were very interesting. I should like to stress the fact that we saw ceroid in the chromidrotic glands in small amounts, and we take the view that ceroid is a part of the general picture of the lipofuscins—that is, the fat is oxidized initially to ceroid and then goes on progressively to higher states of oxidation. Hence we were not surprised to find that the ceroid or waste pigment was present in these chromodrotic glands.

As to the last point, comparative physiology is extremely interesting in this problem of chromidrosis. We also studied the hippopotamus, at a small risk, at the Philadelphia zoo. Although we have never obtained any biopsy, that has been secured by others, and an apocrine type of gland has been found to be responsible for the reddish material that the hippopotamus secretes.

An excellent book appeared in Germany in the last 10 years, which has not received any attention in this country, a monograph of 400 or 500 pages, by a man named Schaffer, a histologist who spent his life studying the glands of the skin of all mammals from the standpoint of comparative anatomy and physiology. In that book (Die Hautdrüsenorgane der Säugetiere, 1940) is a wealth of material on comparative physiology and anatomy of the skin. He points out that the elephant, for instance, has a gland near the eye which secretes a reddish pigment at times of sexual excitement.

Another final point about comparative physiology is the fact that bloody tears, red tears, have been observed probably by many of you in rats which have been subjected to rather critical stresses; that is, whenever rats are placed in a real stress situation, they will produce bloody tears, and this is due to the production of a red-colored porphyrin by the Harderian gland. It is interesting that this chromodacryorrhea has been shown very definitely to be due to a porphyrin and not to be due to anything similar to the product we found in our studies.

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ATTEMPTS TO ISOLATE A VIRUS FROM PEMPHIGUS FOLIACEUS CASES

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THE ETIOLOGY of the diseases or syndromes of the pemphigus group is a challenging subject which remains undisclosed despite the large volume of research done upon it. The number of theories on the cause of pemphigus is a good index of the tremendous confusion prevalent not only in the etiology, but in the pathogenesis, epidemiology, and other domains of the knowledge on pemphigus as well. The existence in the literature of rather numerous reports of isolation of a virus from pemphigus vulgaris cases * as well as several suggestive observations on pemphigus foliaceus [4] motivated the work reported here.

Attempts to isolate a virus from pemphigus foliaceus material are apparently found only in the Brazilian literature which is explainable by the relative abundance of cases in Brazil. Lindenberg [5] was the only worker who reported success, but his work is open to criticism due to poor technique and small number of animals employed. Artigas and Mourão [6] repeated Lindenberg's work under satisfactory conditions and failed to reproduce his results.

The endemic incidence of pemphigus foliaceus in Brazil † affords unusual facilities for work on the experimental reproductibility of this disease. The identity of pemphigus foliaceus as it occurs in Brazil with the classic pemphigus foliaceus which occurs in Europe and the United States of America, for instance, is now beyond doubt. The disagreement which once existed on this identity has been shown † to derive from an incomplete search of the literature as well as from uncritical appraisal of facts. Much speculation has been done on whether pemphigus foliaceus, pemphigus vulgaris, pemphigus vegetans, and pemphigus erythematosus are definite diseases or just syndromes of the disease pemphigus.

In the work reported here, emphasis was put on improving the technical conditions and controls of previous work. The mouse brain and chick embryo chorioallantois were selected for the initial work because these two tissues are known, according to a great deal of experience, to be capable of supporting the multiplica-

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* See references 1, 2, and 3.

† Reference 4, and Angulo, J. J.: Bibliography of "Fogo Selvagem" (Wild Fire) or Pemphigus Foliaceus Endemic in Brazil, unpublished data.

tion of numerous viruses, thus becoming standard media in virus isolation. Unfortunately, circumstances beyond my control prevented extension of the work to hosts and inoculation routes other than those just mentioned.

MATERIALS AND METHODS

Inocula were prepared from samples collected from patients attended at the hospital of the Pemphigus Foliaceus Service of the state of São Paulo where this disease is endemic.† All cases were examined by at least three physicians from the Service staff who had had ample clinical experience with pemphigus foliaceus.

The starting material for inoculation consisted of nine samples of blister fluid obtained from six patients; two samples of the skin layers externally lining blisters from two patients; one sample of blood serum from one feverish patient; one sample of blood coagulum from the latter patient; one biopsy from an erythrodermic exfoliative lesion from one patient, and five samples of spinal fluid from five patients. Thus 13 samples were obtained from early lesions or acute episodes, while the biopsy and the 5 spinal-fluid samples were obtained from cases in the characteristic, chronic stage of the disease. The 19 samples from 13 patients were used in a total of 176 intracerebral passages in mice, while 16 of these 19 samples were used simultaneously with the mouse passages in a total of 159 chorioallantoic passages in the chick embryo.

The total of 1,225 Swiss-strain mice was employed as follows: Intracerebral inoculations of 0.03 and 0.02 ml., respectively of a 10^{-1} suspension of pemphigus foliaceus material were given to 944 adult and 90 young mice. One hundred and ninety-one adult animals were used as controls in the following groups: 25 mice inoculated intracerebrally with 10^{-1} suspension of normal mouse brain; 18 mice inoculated intracerebrally with the suspending fluid alone; 13 mice punctured in the brain but without inoculum injection, and 135 uninoculated mice.

Usually 9- to 10-day-old eggs of Leghorn hens were used throughout the experiments. Four to 5 eggs were inoculated in each passage. The standard Burnet technique for chorioallantoic inoculation was employed, using 0.5 ml. of 10^{-1} suspension of inoculum. In egg, as well as in mouse passages, 10^{-2} and 10^{-3} suspensions were occasionally inoculated in addition to the regular 10^{-1} suspension.

Experiments using control eggs inoculated with normal human skin or the suspending fluid were not made, since specific lesions of the chorioallantois are not expected in these cases, according to ample experience. Furthermore, the chick embryo, unlike the mouse, is not known to harbor interfering, enzootic viruses.

The inoculum-suspending fluid consisted of a 10% solution of horse serum in normal saline solution to which penicillin, streptomycin, and crystal violet were added in the proportions suggested by McNair Scott[7] for prevention of the bacterial and fungal growth which may be expected from a skin inoculum, even from one from normal skin. This precaution had not been taken in previous work. Control of contamination was made by culturing 0.5 ml. portions of the inoculum in blood-agar plates and thioglycolate-broth tubes.

COMMENT

In only 2 out of the 176 mouse passages were illness and death observed in rates suggestive of the existence of an infectious agent. However, these positive passages are meaningless from the standpoint of the experimental reproduction of pemphigus foliaceus, since the uninoculated mouse batches observed simultaneously showed the same incidence, the same kind of signs and symptoms, and essentially the same death rates. This was apparently due to epizootic episodes.

In 15 out of the total 159 egg passages chorioallantoic lesions were observed. In 6 of these 15 passages there was unmistakable evidence of the traumatic origin of the lesions. In the remaining nine passages lesions were found only in occasional eggs from a given passage, and they were not observed in the successive passages of the membranes showing these lesions.

The results presented in the preceding two paragraphs indicate that the pemphigus foliaceus samples which were tested did not contain an agent cultivatable in the mouse brain or chick-embryo chorioallantois. This evidence together with the evidence obtained by Artigas and Mourão,[6] Vieira and Mourão,[9] Mourão,[10] and Travassos ‡ clearly indicate that reliable proof of the existence of a transmissible agent in pemphigus foliaceus cases has not been obtained yet, despite the large number and varied nature of samples inoculated through different routes in various animal species.

In the case of pemphigus foliaceus, as well as in that of pemphigus vulgaris,[11] it may be noticed that whenever attempts to isolate a transmissible causative agent have been made under adequately designed and executed experimental conditions the results have been negative. Furthermore, poor technical conditions and/or lack of adequate controls are features common to reports of successful isolations. However, the possibility of the existence of an agent uncultivatable by the usual techniques and in the common experimental hosts has not been ruled out yet. The etiology of the pemphigus group of diseases or syndromes thus remains unsettled, without any definite, promising lead.

SUMMARY

Nineteen samples from 13 cases of pemphigus foliaceus were used in a total of 176 mouse intracerebral passages and 159 chick embryo chorioallantoic passages, with negative results.

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BASAL CELL EPITHELIOMAS OF THE SOLE

A Report of Two Cases

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THE FIRST case of basal cell epithelioma of the sole described in this paper came to our attention in 1948; the second some three years later. The second encounter with this most unusual localization for a basal cell epithelioma prompted this report. It is felt that these cases are of interest not only because of their rarity but also because of the light they may shed on the disputations concerning the histogenesis of basal cell tumors.

We inquired of a number of our colleagues as to their experience with basal cell tumors of the sole (or palm) and a search was made of the literature for earlier reports. Dr. Herman Beerman was good enough to tell us of a case he studied histologically some years ago. Dr. Hamilton Montgomery and Dr. Fred Weidman, however, were not able to recall any despite their vast experience.

Statistics attest to the fact that the face is the area of predilection for these tumors and that "basal cell epitheliomas are more frequently found about the head than any other part of the body." Broders in one of the earliest reports on the localization of basal cell tumors showed that 90.7% of a series of 268 of these tumors occurred on the face; Owen found 92.58% of the lesions on the face and head in 836 cases observed at the Mayo Clinic from 1915 to 1927; Beck reporting on a group of 88 cases found only nine outside the face; Wilson in a group of 410 cases (which included Broders' material) found 97.7% above the clavicle, and most recently Elliott and Welton in a study of 1,928 epitheliomas of all types (of which 381 were examined histologically and 48.8% were of the basal cell variety) found 77.8% of all lesions on the face.

Statistics also show that the extremities are relatively uncommon sites for these tumors. In the various series already referred to, Broders found 0.74% on the extremities; Beck found one out of 88 cases on the hand and one on the leg; Wilson found less than 1% on the leg and foot. To these one may add the report of Torrey and Levin who found 10 out of 962 (1%+) on the upper extremity and 1 out of 962 (0.1%+) on the lower extremity.

Beck contended that when basal cell epitheliomas are found on the extremities they are more likely to be found on the hands and legs than on other parts and

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From the Department of Dermatology and Syphilology of the New York University Post-Graduate Medical School (Dr. Marion B. Sulzberger, Chairman) and the Skin and Cancer Unit of the New York University Hospital.

more often on the hands than on the legs. This is borne out by the study of Sachs and Garbe who found nine on the hands, six on the legs, five on the thighs, four on the forearms, three on the arms, two on the wrists, two on the ankles, one on the finger and one on the feet (two lesions were present in one case) in a group of 32 cases of primary basal cell epitheliomas of the extremities. Hazen on the other hand reported on 10 basal cell cancers of the extremities and found them to be distributed as follows: lower part of the leg, four; upper part of the arm, two; hand, one; finger, one; thigh, one, and ankle, one.

No mention was made of palmar or plantar lesions in the reviews referred to thus far, including those dealing primarily with the localization of basal cell tumors. The exact site of the tumor was not always indicated, but when the position was noted it was invariably on the dorsal aspect of the hand or foot. This was also true of the reviews and the individual case reports of others. None of the tumors in the series reported by Sachs and Garbe was on the palm or sole.

The total yield of a careful survey of the literature was a single reference to a basal cell epithelioma of the sole (and none of the palm). This was a report by Schreiner and Wehr who found one basal cell tumor on the sole near the heel among 37 cases of primary malignant tumors of the foot.

Although some observers have maintained that "hardly any part of the body surface is exempt" or that basal cell epitheliomas may occur in the skin of any part of the body none of these writers mentioned the palms or soles specifically. On the contrary, Lever stated unequivocally that "basal cell epitheliomas may occur anywhere in the skin except on the palms and soles." Guy, in a discussion of Haythorn's paper on the histogenesis of basal cell epithelioma also questioned the existence of basal cell epitheliomas in these areas.

REPORT OF CASES

Case 1.—T. P., a woman aged 38, consulted one of us (F. P.) on Nov. 18, 1948, because of an "infection" of three years' duration of the right sole. There was no history of trauma antedating the appearance of the lesion, nor had the patient taken arsenicals to her knowledge. Various medicaments were used in the treatment of the lesion, including potassium permanganate soaks and a number of different ointments without any appreciable change. Some months after the lesion first appeared on the sole, the patient became aware of another "growth" on the dorsum of the right hand.

A fungating, sessile, moist and soft, dusky red tumefaction measuring approximately 1.5 cm. in diameter, with a millimeter-sized area of deep brown pigmentation at the distal pole, was found to the left of center of the right sole. Another lesion, approximately 1 cm. in diameter, was located over the fifth metacarpal on the dorsal aspect of the right hand. The latter was sharply marginated, violaceous in color except for some minute specks of hyperpigmentation and two small crusted areas near the center of the lesion.

Nevocarcinoma, granuloma pyogenicum and idiopathic hemorrhagic sarcoma (Kaposi's sarcoma), in order of their probability, were the diagnoses entertained as the most likely for the lesion on the sole. There was little doubt that the lesion on the hand was a basal cell epithelioma.

Histologic examination of a biopsy specimen taken from the growth on the sole disclosed many irregular but well-defined masses of basal cells in the upper and midcorium, tapering off in the deep corium. There were no notable changes in the epidermis except for an ulcerated zone. No histologic diagnosis other than basal cell epithelioma was possible, despite the unusual localization of the lesion.

The Sherwell technique (curettage under procaine hydrochloride [Novocaine] anesthesia and application of acid nitrate of mercury solution [N. F. IV] followed by neutralization with sodium bicarbonate) was used to destroy the lesion. Healing progressed uneventfully.

The patient failed to return for treatment of the lesion on the hand until Dec. 3, 1951. Despite the lapse of time there was no apparent macroscopic change in the lesion on the hand. Reexamination of the treated site on the sole disclosed a soft superficial flexible scar. It was at this time that she first called attention to an erythematous somewhat nodular and hyperpigmented lesion on the anterior aspect of the left thigh. The pigmentation was most distinct at the border of the lesion, which was also pearly and somewhat elevated. The clinical features were those of a basal epithelioma.

A biopsy specimen from the lesion on the hand was taken prior to the destruction by the Sherwell method. The clinical diagnosis of basal cell epithelioma was confirmed on histologic examination. Microscopic changes included many irregular masses of basal cells of varying size and shape scattered throughout the corium. Some disturbance of the connective tissue framework was noted as well as several dilated blood vessels. Pigment was found in the upper corium.

The lesion on the thigh was destroyed in the same manner a few days later. Examination of a specimen taken prior to the destruction of the tumor disclosed essentially the same microscopic findings as were found in the lesions on the sole and hand.

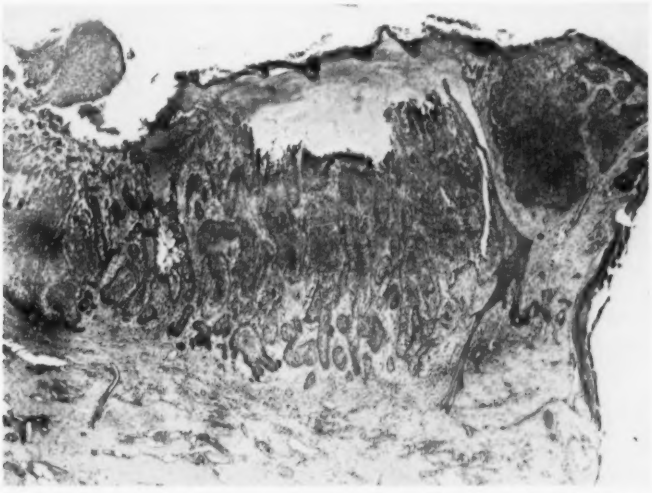

Fig. 1 (Case 1).—Basal cell epithelioma of the sole showing downward growth of basal cells in solid nests. × 33.

There was no evidence of a recurrence at any of the treated sites over an observation period of five years after treatment.

Case 2.—A. L., a woman, aged 62, was first seen at the New York Skin and Cancer Unit of the University Hospital on Oct. 16, 1951. She complained of a "growth" of two years duration that failed to respond to topical medication on the right sole. The patient volunteered the information that a crust would form from time to time which separated every few weeks leaving a moist oozing surface. There was no history of trauma, nor did the patient knowingly take arsenicals.

Examination revealed a dime-sized, slightly elevated, well-defined, violaceous, firm lesion with a moist surface on the plantar aspect of the right foot. A tentative diagnosis of granuloma (type?) was made. Inspection of other parts of the body disclosed no significant changes.

Histologic examination of the lesion revealed intensely basophilic circumscribed and linear masses of basal cells in the corium extending down into the lower third. These cord-like masses appeared to come off at several points along the basal margin of the epidermis. The

Fig. 2 (Case 2).—Basal cell epithelioma of the sole. Note the moist granulomatous-like appearance of the lesion.

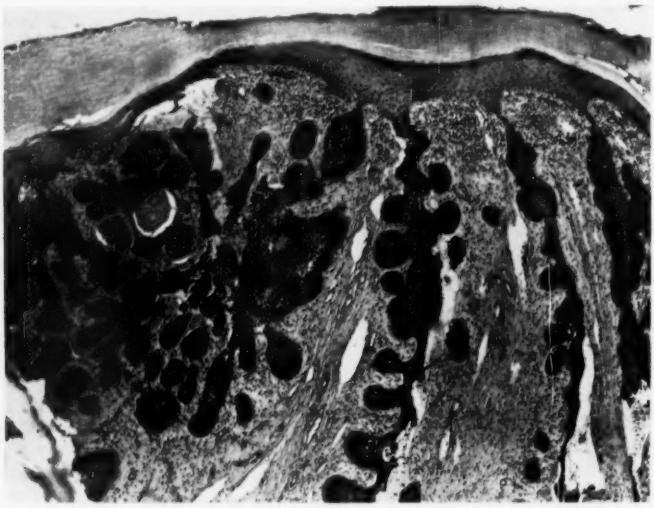

Fig. 3 (Case 2).—Basal cell epithelioma of the sole showing solid nests and glandular tube-like strands of basal cells arising at multiple points at the basal cell layer of the epidermis. × 44.

strands were irregular in outline, consisting at some points of two to four layers of cells, at others of many more. The cellular masses springing from the cord-like stems were circumscribed and teat-like extending from either side of the main stalk for a variable distance into the surrounding connective tissue. These bulbous outgrowths were composed entirely of basal cells, and in some areas these aggregates were limited by a row of columnar cells arranged in a characteristic palisade manner. The connective tissue surrounding the masses was denser than normal with scattered fibroblasts and a few small round and wandering connective tissue cells. The superficial vessels were dilated and the overlying epidermis was irregularly and moderately acanthotic.

Serial sections of the biopsy specimen did not disclose any aberrant epidermal appendages or epidermal cell rests or any connection of the cellular masses with the sweat glands. No lumens were seen in these closely packed groups of cells. Neither could myoepithelial cells be demonstrated with Masson's trichrome stain.

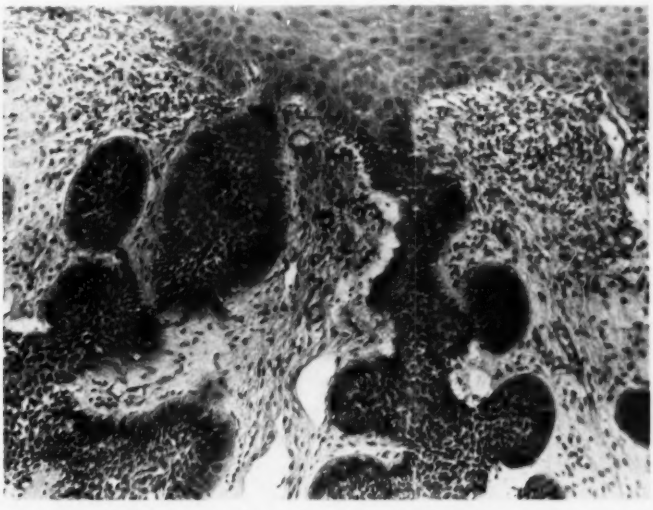

Fig. 4 (Case 2).—Tube-like strands of basal cells showing bulbous outgrowths from either side of the main stem. The outgrowths are composed entirely of basal cells limited by a row of columnar cells arranged in a characteristic palisade manner. × 124.

A histologic diagnosis of basal cell epithelioma of the sole was made.

Total excision and serial sections of the lesion were contemplated to permit further study. Regrettably, the patient refused consent and was not seen again after Nov. 13, 1951.

COMMENT

Two cases of basal cell epithelioma of the sole have been presented. In neither case was the diagnosis made on clinical grounds nor was the possibility of basal cell carcinoma entertained in the clinical differential diagnosis. This is understandable in view of the unsual localization and the moist granulomatous appearance of the lesions. Both patients were women, one in the late thirties, the other in the early sixties. In one (T. P.) the lesion on the sole was associated with a typical rodent ulcer on the dorsum of the left hand and a typical pigmented basal cell epithelioma on the anterior aspect of the left thigh.

Histologic examination in Case 1 disclosed solid nests of basal cells, in a pouch-like downward growth from the epidermis, apparently unicentric in origin, corresponding to the carcinoma basocellular solidum of Krompecher. The histopathologic picture was essentially the same as in the lesions removed from the hand and thigh.

The sections in Case 2 disclosed a basal cell epithelioma made up of solid masses and irregular strands of basal cells arising from multiple points in the epidermis and extending deep into the cutis. The anatomic configuration was that of a multicentric tumor arising directly from the basal cell layer of the epidermis. Although the penetrating elongated strands with bulbous outgrowths were reminiscent of glandular, tube-like structures, serial sections of the biopsy specimen failed to disclose any apparent connection with the sweat apparatus or any resemblance to sweat epithelium.

It may be presumptuous to speculate about the significance of these cases in the controversial question of the histogenesis of basal cell tumors. Yet, it would appear that they may have a bearing on the problem. It seems reasonable to state that in these two cases, at least, the site of origin could not possibly have been the hair follicles or sebaceous glands since the soles are completely devoid of these structures; nor the apocrine glands which, although found in outlying places on occasion, e. g., the hypogastrium, forehead and cheeks have never, to our knowledge, been demonstrated on the palms or soles. Thus, the basal cell layer of the epidermis, the sweat ducts and epithelial cell "rests" in the corium remain the only possible points of origin. In neither tumor, however, did the microscopic picture resemble the type of adnexal carcinoma arising from eccrine sweat glands described by Foot and Adamson. Although one cannot disregard Virchow's theory of cell "rests," or Cohnheim's concept of arrested embryonic cells, or Hazen's thesis of congenitally displaced epithelial sturctures or Adamson's proposal of aroused embryonic foci as possible sources for the epitheliomas, it does seem more plausible in the second case (A. L.), at least, in view of the multicentric type of lesion, to hypothesize that the lesion stemmed directly from the basal cell layer of the epidermis.

The cases herein reported appear to lend support to those observers who maintain that basal cell tumors arise from the basal cell layer of the epidermis, and, although they may, they do not necessarily originate from "distorted primordia of dermal adnexa," or from hair matrices ("hair-matrix" carcinomas), or from hair sheaths, or from various dermal appendages or from arrested embryonal cells of the primary epithelial germ.

SUMMARY

Two cases of basal cell epithelioma of the sole, a rare localization, are described in detail. The possible significance of these cases in the controversial question of histogenesis is discussed, and the various theories as to the origin of basal cell epitheliomas are briefly reviewed.

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HEXYLCAINE IN MANAGEMENT OF PRURITIC DERMATOSES

Clinical Evaluation of New Local Anesthetic

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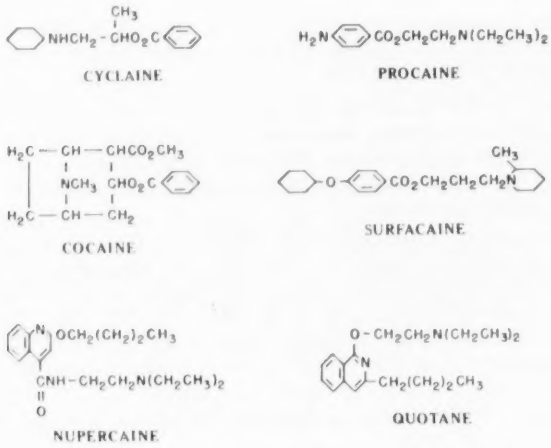
PRURITUS is undoubtedly the most frequent of all the subjective complaints of the patient who seeks dermatological consultation. The etiological factors involved in the production of discomforting pruritus are manifold.

The value of local anesthetics has been ascertained in the alleviation of the discomfort which is experienced in the pruritic dermatoses. I hereby describe my experiences with a new local anesthetic, namely, hexylcaine hydrochloride.



Chemical formula of the popular local anesthetics.

Hexylcaine hydrochloride is the abbreviated generic name for 1-cyclohexylamino-2-propylbenzoate. It is noted that the amino group is not in the para-position of the benzene ring. The proprietary name for this product is Cyclaine.

Pharmacological and clinical studies were carried out by Beyer and others, Ruben and Anderson, and Orkin and Rovenstine. These investigators established its low toxicity and therapeutic index. Ruben and Anderson, and Orkin and Rovenstine found it an effective agent in spinal anesthesia and nerve block.

Hexylcaine (Cyclaine) was supplied by Dr. G. Bayne and Dr. S. Clyde Strickland of Sharp & Dohme, Inc., Medical Research Division, West Point, Pa.

Hexylcaine has a molecular weight of 297.85 and is freely soluble in water. A 1% aqueous solution has a pH of 4.4 (unbuffered) and is stable under the usual sterile procedures of boiling and autoclaving. It does not discolor after long periods of shelf life.

I have been evaluating hexylcaine ointment and lotion for the past two years for the relief of pruritic dermatoses in 258 patients. I have tabulated the dermatitis, the number of patients treated, and the relief obtained (Table).

The hexylcaine ointment used in these studies contains hexylcaine hydrochloride, 2%, dispersed in a water-washable cream.

The hexylcaine lotion is composed of 2% hexylcaine in a zinc oxide, talc, glycerin, and ethyl alcohol emulsion.

Results of Use of Hexylcaine Preparation in the Following Dermatoses

Diseases	Cases Treated, No.	Improved	Unimproved
Dermatitis venenata			
Occupational, chemical, plants, trauma	64	58	6
Pruritus ani	16	13	3
Pruritus vulvae	22	18	4
Senile pruritus	8	7	1
Neurodermatitis			
Disseminated	27	23	4
Lichen vidal	12	10	2
Dermatitis hemostatica	6	5	1
Herpes zoster	12	10	2
Dermatitis calorica	16	15	1
Vesicular eruption			
Hands	15	11	4
Reaction to penicillin	8	7	1
Epidermophytosis pedis	11	9	2
Miliaria	21	19	2
Neurotic excoriations	6	5	1
Lichen planus	8	7	1
Dermatitis herpetiformis	6	3	3
Totals	258	220	38

The ointment and the lotion do not contain menthol or phenol because I wanted to determine the therapeutic efficiency of the hexylcaine preparation without the addition of any cooling or antipruritic agents. The studies have been continuing for over a period of two years.

Of the group of patients treated, there was no evidence of any eczematous allergic sensitization due to the hexylcaine preparations.

Eighteen patients who had a known eczematous allergenic sensitivity to ethyl aminobenzoate (Benzocaine) or paraphenylenediamine were also given patch tests to determine whether any cross sensitization existed. It was found that no cross sensitization existed with hexylcaine, indicating its practical use.

Two hundred patients with normal skin were selected at random. These patients were given patch tests with hexylcaine ointment and hexylcaine lotion. These patients had no known sensitivity to external contactants. These tests were performed to ascertain whether primary sensitization to hexylcaine existed. The retest, 14 days later, was conducted to determine the production of allergenic

sensitization. The results of this survey indicated that the hexylcaine ointment and lotion produced no irritating primary sensitization or secondary allergenic untoward effects.

The hexylcaine ointment is compatible with various other therapeutic indicated preparations. I have prescribed equal parts of hexylcaine ointment with 10% crude coal tar paste, 10% ammoniated mercury paste, 3% iodochlorhydroxyquin (Vioform) cream, and hydrocortisone ointment. In this manner, the associated pruritus is relieved, and the clearing of the dermatitis is made more rapid. Superficial x-ray therapy can also be used simultaneously.

There was a stinging sensation, probably due to the alcohol content, when the hexylcaine lotion was applied to four patients who had denudation of the skin in the vesicular dermatoses. However, as the therapy continued, the discomfort disappeared. In the chronic dermatoses, the character of the disease is not altered but with the diminution of itching the lichenification becomes lessened. The relief of itching has been reported to exist from one to three hours. When the ointment is used and rubbed into the skin, the relief seems to last longer than when the lotion was prescribed. The lotion, because of its drying action, is indicated in the moist dermatoses.

Lynch advocates the use of Quotane (1-[β-dimethylaminoethoxy]-3-*n*-butylisoquinoline monohydrochloride), one of the newer antipruritic agents, as a relief of pruritus due to cutaneous disorders. Lynch observed that relief was obtained in 60% of 258 therapeutic applications. Some relief was further obtained in an additional 20% of patients. Corson found Quotane of value in 84% of patients under his dermatological care.

Lane has devoted a publication to treatment of therapeutic dermatitis. He cites many cases of sensitization dermatitis due to ethyl aminobenzoate and related derivatives which have been incorporated in proprietary ointments. He suggests that continued emphasis on the possible danger of these sensitizing agents may aid in diminishing the frequency of unsupervised usage.

Grolnick has recently reported a severe reaction following the continued inunction of Quotane ointment. He stated that after the patient had improved with bland local therapy, she was given a patch test and was found to present a third-degree reaction to Quotane. There was a third-degree reaction to butamben (Butesin) picrate and ethyl aminobenzoate, showing the role of possible cross sensitization to related chemicals.

I have observed that when a new therapeutic agent is initially introduced on the therapeutic horizon the sensitization factor is very low. However, with continual use of the agent, contact dermatitis begins to be observed and finally case reports crop up in the literature. If the chemical radical which is known to be the cause of the sensitization is substituted in another position, then the index of sensitization becomes very low.*

* During the past six months, I have been clinically evaluating the antipruritic effect of a 5% hexylcaine preparation in a water-washable base in 56 cases of pruritic dermatosis. The relief of pruritis extends for about four hours. No evidence of sensitization has been observed in these patients. The onset of relief occurs almost instantaneously after the topical application of the hexylcaine cream.

SUMMARY AND CONCLUSIONS

I have clinically evaluated a new local anesthetic, hexylcaine hydrochloride (1-cyclohexylamino-2-propylbenzoate) (Cyclaine) in 258 cases of pruritic dermatoses.

Satisfactory relief was obtained in 220 patients. Thirty-eight patients stated that the relief was of temporary effect and did not aid their discomfort.

Patch tests of the hexylcaine preparations on 200 patients, selected with no known sensitization to external contactants, revealed no primary sensitization or secondary allergenic response.

No cross sensitization exists between hexylcaine and patients who are sensitive to ethyl aminobenzoate (Benzocaine) or paraphenylenediamine.

Hexylcaine ointment and lotion have an extremely low sensitization index.

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FIBROSING BASAL CELL EPITHELIOMA

A Study of Its Morphological Features, Relationship to Basosquamous Epithelioma and Differentiation from Prickle Cell Carcinoma

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AND
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MOST AUTHORITIES now agree that the ubiquitous basal cell epithelioma is derived not from basal epidermal cells which are the parents of prickle cells but from specialized epidermal cell rests which are the potential progenitors of skin appendages. Complicated classifications of basal cell tumors based upon the degree and type of cellular differentiation are intriguing, but of questionable practical significance. Numerous investigators, particularly among the British, have demonstrated little correlation between histological features and clinical behavior or radiosensitivity. Of greater importance is the differentiation of basal cell epithelioma from prickle cell carcinoma. Histological identification usually can be accomplished without equivocation, but on occasion this may be difficult, and basal cell epitheliomas which exhibit marked fibrosis are prone to cause such difficulties. The presence of desmoplasia in recurrent or irradiated basal cell epitheliomas is well known, but its occurrence in untreated tumors has received little attention.

The histological sections from an unselected group of 80 basal cell epitheliomas from the files of the department of pathology of the St. Albans Naval Hospital were reviewed. In this group there were eight tumors which exhibited significant degrees of fibrotic reaction. Only one of these was a recurrent lesion, and none had been subjected to radiotherapy. Their clinical appearance, location, and degree or type of histological differentiation did not differ significantly from those which did not show desmoplasia.

There was no correlation between the presence of fibrosis and the type of adnexal cell differentiation. Several of the tumors exhibited pilar or cystic features (Figs. 1, 4, 5, 6, and 8), while others were of the undifferentiated variety (Figs. 10 and 13).

Two predominant types of tumor cells were noted. They were usually not intermingled within the same foci but were present as the only type within a given tumor area. The first was a distorted, elongated cell, with a spindle-shaped nucleus which stained very intensely, apparently because the chromatin was so compressed within

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The opinions and/or assertions contained herein are those of the authors and are not necessarily to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

From the Department of Pathology, United State Naval Hospital, St. Albans, Long Island, N. Y. (Commander Umiker); Civilian consultant in dermatology to the United States Naval Hospital (Dr. Director).

Fig. 1. (Case 1).—Typical cystic basal cell epithelium showing broad retraction spaces on the left and pseudoepitheliomatous hyperplasia of the overlying epidermis; × 70.

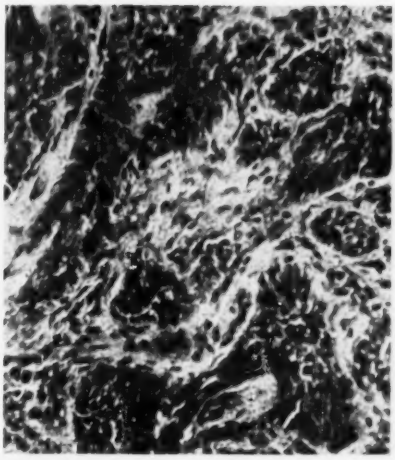

Fig. 2 (Case 1).—Another portion of same tumor showing desmoplastic reaction. The tumor cells are of the small, hyperchromatic cell type; × 240.

Fig. 3 (Case 1).—Area at base of same lesion showing infiltrating filaments of neoplasm which have not yet excited any reaction; × 150.

Fig. 4 (Case 2).—Fibrosing basal cell epithelioma with pilar type differentiation. Note the keratin nests in the lower portion. × 90.

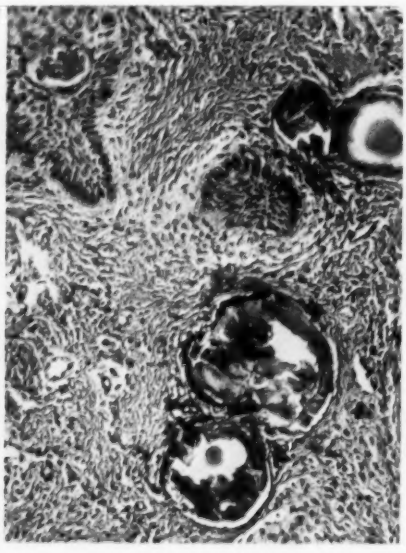

Fig. 5 (Case 2).—Keratin nests showing calcification. Compare these and those in Figure 4 with the epithelial pearl of prickle cell carcinoma in Figure 7. × 115.

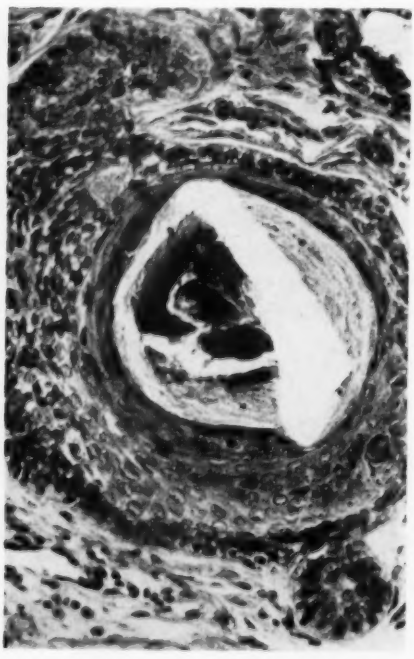

Fig. 6 (Case 2).—Relatively well differentiated hair follicle including hair shaft; × 242.

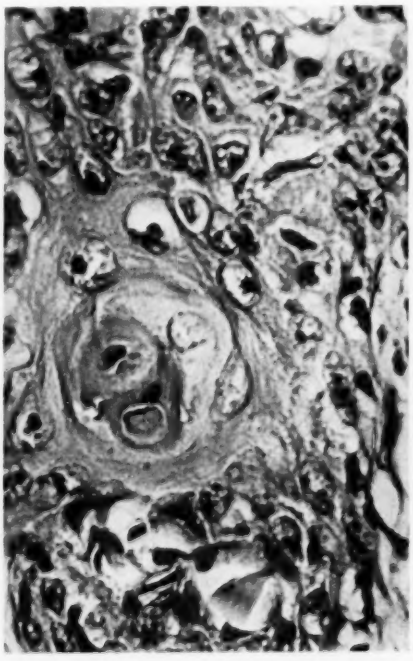

Fig. 7.—Epithelial pearl from a case of prickle cell carcinoma. Compare with keratin nests in Figures 4 and 5. × 460.

Fig. 8 (Case 3).—Another fibrosing basal cell epithelioma of pilar type. Note the combination of small, hyperchromatic cells with large pale cells. × 180.

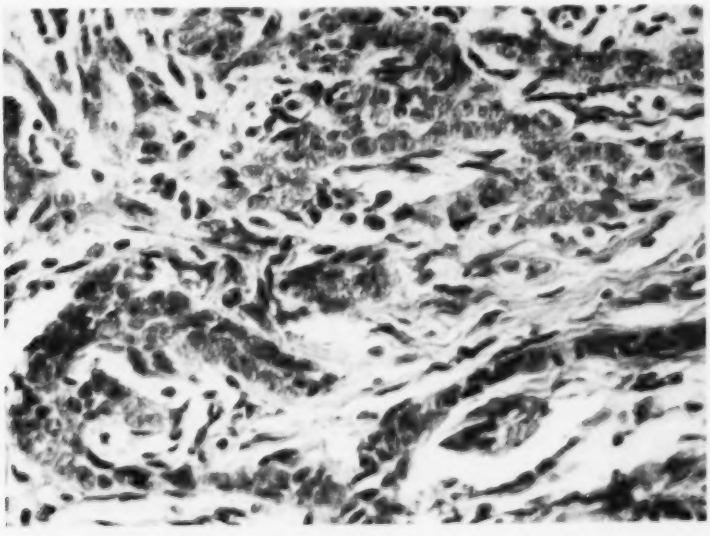

Fig. 9 (Case 4).—Fibrosing basal cell epithelioma. Areas such as this are occasionally misdiagnosed as plexiform or prickle cell carcinoma. The tumor cells are the large, pale type. Note the uniformity of the cells and the persistence of retraction spaces. × 300.

narrow confines. The cytoplasm was also compressed, distorted, and hyperchromatic (Figs. 2 and 10). Such appearance was particularly pronounced at the peripheral areas of the tumors, where the fibrotic reaction of the corium was most noticeable, or where the columns of the tumor were most bizarre and irregular. The second type of tumor cell was seen more frequently away from the periphery of the tumor, where fibrosis and compression were least pronounced. These cells generally comprised the minor portion of the neoplasm. The clusters of these cells were rounded or irregularly ovoid and were frequently small. There was not the usual well-defined outer limiting, cuboidal or columnar "basal" layer, and the cells were relatively larger and paler staining than those in the distorted regions. The nuclei were large, round, and relatively pale staining, because the chromatin granules were dispersed in nonstaining parachromatin spaces to produce a vesicular appearance (Figs. 9 and 11). Intermediate gradations between these two extremes were found.

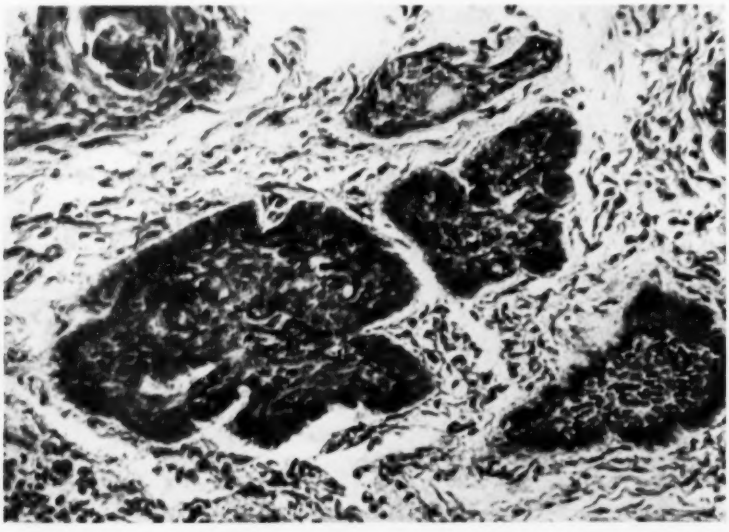

Fig. 10 (Case 4).—Another area from same tumor showing islands of typical undifferentiated basal cell epithelioma. × 260.

The extent of the fibrosis was variable even within individual tumors. Large, cellular neoplasms exhibited the least desmoplasia, while those consisting of narrow strands or small clusters of cells frequently revealed marked fibrous reaction (Figs. 4, 8, 9, and 11). The fibrosing process resembled that seen in scirrhous carcinoma rather than that seen in lesions such as fibrosing adenosis of the breast or sclerosing hemangioma of the skin. In other words, it appeared to be a stromal response to the tumor rather than an integral part of it. Occasionally, it was possible to demonstrate infiltrating naked tumor strands at the base or lateral borders of the tumor (Fig. 3), while fibrous cuffs surrounded similar neoplastic trabeculae in central and probably older areas (Fig. 2). This suggested that the desmoplasia was a response to invasion. Whether or not it represented a property of the neoplasm or of the host tissue could not be determined.

The usual basal cell epithelioma with mild associated fibrosis presents no diagnostic difficulties. However, those lesions characterized by a uniformly scirrhous appearance and unicellular strands or clusters may be less readily recognized as basal cell epitheliomas (Figs. 2, 9, and 11). Foot has commented on this problem and suggested that some of these tumors are not basal cell epitheliomas but plexiform epidermoid carcinomas. Others resolve this diagnostic dilemma by classifying such tumors as basosquamous epitheliomas. This is understandable in view of the combination of separate foci of small, hyperchromatic cells, which are correctly interpreted as the "basal" cell component, and foci of larger, paler cells, which are incorrectly interpreted as prickle cells. The same interpretation may be made when the large, pale cells constitute the entire neoplasm, as they appear to represent cells intermediate between basal and prickle cells. While it is not the purpose of this paper to discuss the controversial status of basosquamous cell epithelioma, it is our opinion that if lesions such as we have just described and basal cell epitheliomas which excite a pronounced pseudoepitheliomatous hyperplasia (Figs. 1 and 12) are excluded, very few basosquamous tumors remain. Full appreciation of the histological appearance of fibrosing basal cell epithelioma will avoid incorrect interpretations. Careful examination of multiple sections will usually reveal sufficient characteristics of basal cell epithelioma to enable a correct diagnosis. Prickle cell carcinoma seldom possesses the cellular uniformity seen in these lesions. The presence of retraction spaces is helpful in this respect. While they are not as prominent as in highly cellular basal cell epitheliomas (Fig. 1), these spaces can usually be found in fibrosing basal cell tumors (Figs. 8, 9, and 13), whereas they are rarely, if ever, present in prickle cell carcinoma. The nature of these spaces has not yet been determined. They are thought to be tissue artefacts incident to tissue processing and therefore similar to the so-called perifollicular "cracking off" seen in lymph nodes in giant follicular lymphoma. However, it is possible that the adnexal cells elaborate a substance which produces or contributes to the formation of these spaces. Information is accumulating to indicate that embryonic organs, Graafian follicles, and some transplanted tumors grow by causing depolymerization of ground substance of the connective tissues into more soluble glycoproteins, as indicated by increased taking up of injected Evans blue dye as increased softening and fragility occur. Presumably, connective tissue fibers are also altered or pushed aside. Similar enzymatic action by cells of basal cell epithelioma rather than the action of tissue processing may be the cause of the retraction spaces. Theoretically, it is believed that most, if not all, basal cell epitheliomas arise from cells which are either embryonal rests or have retained their potency for cutaneous adnexal organ formation (sweat and pilosebaceous glands). It could, therefore, be logically concluded that the cells of such tumors would possess the ability to cause solubilizing changes in the surrounding connective tissue, since this is probably the manner in which the normal embryonically developing adnexal skin organs grow downward through the connective tissue of the dermis. The lack of retraction space formation by prickle cell carcinoma cells appears to agree with the theoretical potency of the prickle cell to form only a stratified epithelium which requires no enzymatic action on surrounding connective tissue and ground substance.

At this point, it must be noted that while these retraction spaces usually assist in proper interpretation of a given lesion, they can also cause confusion by simulating lymphatic invasion when they surround a small cluster of tumor cells (Fig. 14).

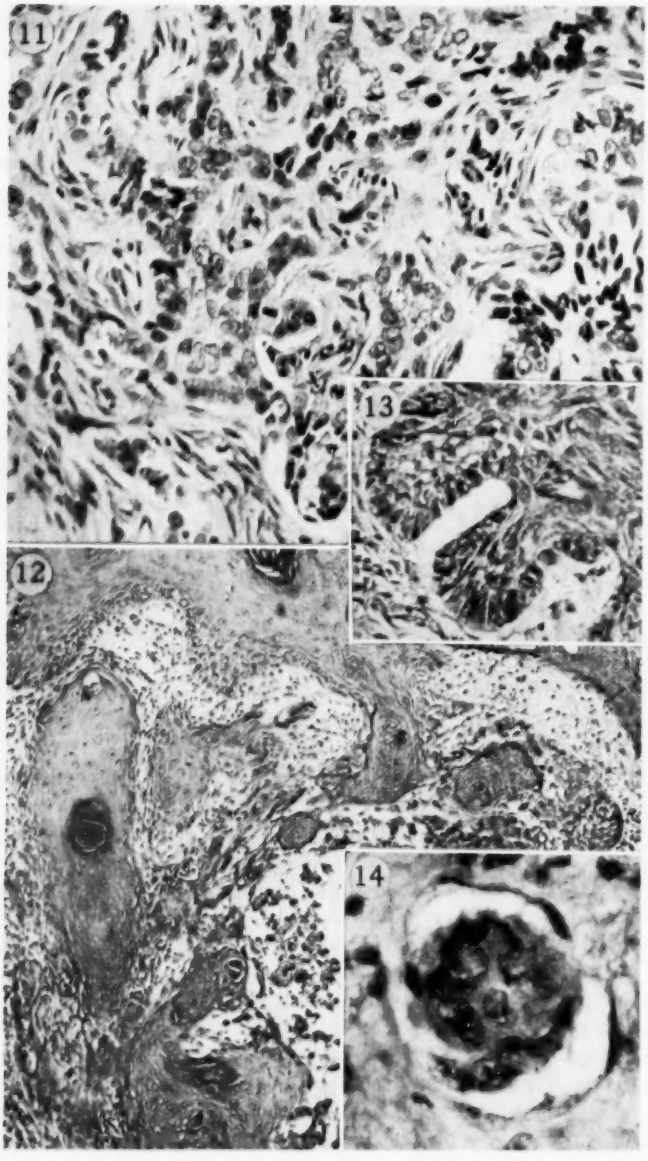

Fig. 11 (Case 5).—Fibrosing basal cell epithelioma with relatively large, pale cells. × 200.

Fig. 12 (Case 5).—Marked pseudoepitheliomatous hyperplasia, which may be mistaken for prickle cell or basosquamous cell carcinoma. × 80.

Fig. 13 (Case 5).—Small area which revealed the basic nature of the tumor. × 180.

Fig. 14 (Case 5).—Retraction spaces giving appearance suggestive of lymphatic invasion. × 484.

Little difficulty should exist in the differentiation between the keratin nests of pilar epitheliomas (Figs. 4 and 5) and the epithelial pearls of prickle cell carcinoma (Fig. 7).

The number of these tumors studied and the length of clinical follow-ups are insufficient to permit any statement as to possible differences in clinical behavior or relative radiosensitivity of fibrosing basal cell epitheliomas and their nonfibrosing counterparts.

CONCLUSIONS

1. Approximately 10% of a small group of basal cell epitheliomas exhibited considerable desmoplasia which was independent of recurrence or radiotherapy.

2. The desmoplastic reaction appeared to be a response to tumor invasion rather than an integral part of the neoplastic process.

3. Fibrosing basal cell epitheliomas occasionally present histological diagnostic difficulties and may be confused with the so-called basosquamous epithelioma or prickle cell carcinoma of skin.

Dr. Umiker's present address is Veterans Administration Hospital, Ann Arbor, Mich.

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Clinical Notes, New Instruments and Techniques

CULTURAL SURVEY OF TINEA CAPITIS IN CENTRAL INDIANA

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ROBERT E. HOLSINGER, M.D.
BYRON H. ARMSTRONG, M.D.
AND
ROSEMARY LOHRMAN, B.S.
INDIANAPOLIS

During the period from January, 1948, to June, 1953, study was made of 454 culturally proved cases of tinea capitis in the dermatology clinic at Indianapolis General Hospital. For the purpose of record, these cases have been reviewed and tabulated. To our knowledge this is the only review of tinea capitis issuing from Indiana in recent years.

The accompanying table demonstrates the relative frequency of the causative organisms. Positive cultures were a prerequisite for inclusion in this Table.

Total Cases of Tinea Capitis Culturally Proved from January, 1948, to June, 1953

Organism	No.	%
Microsporum audouini	396	87.2
Microsporum lanosum (canis)	27	6.0
Microsporum gypseum	12	2.6
Trichophyton tonsurans	10	2.2
Trichophyton mentagrophytes	9	2.0

The percentages in this Table are typical of the urban population of clinic class of patients. According to communication with the staff physicians, the cases seen in private practice have shown roughly 51% caused by Microsporum audouini, 25% by M. lanosum, 10% by M. gypseum, and 14% by T. gypseum in central Indiana.

N. F. Conant confirmed three of the cultures of Trichophyton tonsurans.

From the Department of Dermato-Syphilology of Indianapolis General Hospital, The Alembert Winthrop Brayton Skin and Cancer Foundation and its allied P. C. Reilly Laboratory of Mycology, John Eric Dalton, M.D., Chairman.

DEEP FOREIGN BODY GRANULOMATA

A Reaction to Penicillin

O. S. PHILPOTT, M.D.
A. R. WOODBURNE, M.D.
AND
J. A. PHILPOTT Jr., M.D.
DENVER

Penicillin reactions during the past few years have become more and more frequent. The type of reaction has varied considerably but has been usually of the toxic erythema type or urticarial in nature. Reyer goes so far as to say: "It is entirely possible that the urticarial reaction is the only dermal reaction specific for penicillin." We have made an intensive search of the literature and have been unable to find a case in any way similar to ours.

From the private practice of Drs. O. S. Philpott, A. R. Woodburne, and J. A. Philpott Jr., and the Department of Dermatology, University of Colorado School of Medicine, Dr. O. S. Philpott, Professor.

Fig. 1.—Low power photomicrograph, showing the lack of reaction high up and the granuloma at the junction of dermis and fat and extending deeply into the fat.

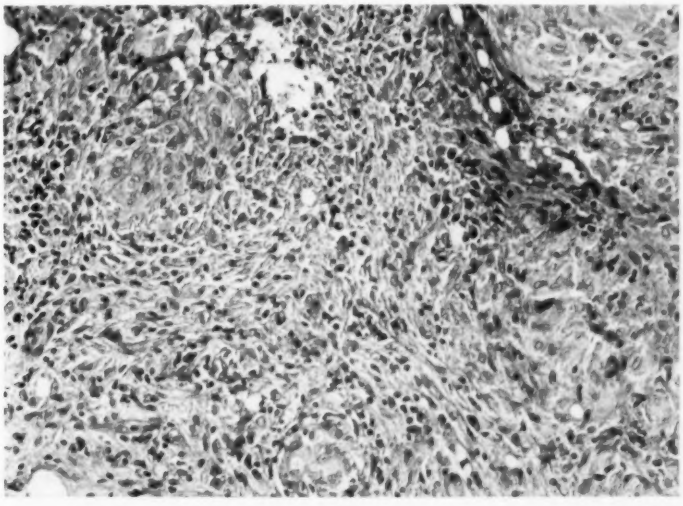

Fig. 2.—Shows the typical sarcoid-like reaction with epithelial whirls, lymphocytes, and giant cells.

REPORT OF A CASE

Mrs. C. H. S., aged 54 was seen in March, 1953, complaining of firm, only slightly tender nodules in the lateral aspects of both upper arms.

The history revealed that in January, 1952, she had received an injection of penicillin in the left deltoid area and that beginning in a few weeks nodules had begun to develop about the site of original injection. They were only slightly tender. The ones closer to the surface were a dusky red. They had remained much the same, gradually diminishing in size and color over the year. In January, 1953, another injection of penicillin had been given in the right deltoid area and within a few weeks nodules similar to those in the left arm had begun to develop. Personal and family history was noncontributory, except that the patient's mother had died of tuberculosis at 53 years of age.

On examination the two arms presented similar pictures. Very slightly erythematous patches could be seen covering much of the upper arms bilaterally. There was a central nodule about 2 cm. in diameter with smaller satellite lesions scattered radially about it. Many of these could not be seen but were felt as pinhead- to bean-sized nodules in the subcutaneous fat. Some of these were as far as 3 in. (7.5 cm.) from the site of injection.

Physical examination was entirely negative except for the nodules. Urinalysis, complete blood cell count, sedimentation rate and chest x-rays were within normal limits. An old tuberculin test was slightly positive in the first dilution.

One of the deep nodules 2 in. (5 cm.) from the site of injection on the right arm was removed for microscopic study.

Microscopic Report.—Dr. Fred Weidman (Philadelphia) made the following comments after reviewing the slides: "The sections show a picture which is decidedly that of sarcoid, what with the exquisitely rounded and sharply demarcated kind of granuloma. Admittedly there are places where there is a large factor of lymphatic infiltration, as where the granulomas are coalescent, and I found two or three granulomas which exhibited early caseation in their centers. I am frank to say that on histologic grounds alone I would have to diagnose sarcoid (better, sarcoid-like reaction in these days when the scope of this reaction has been expanded so much). In any event, the sections do not show tuberculosis."

COMMENT

When we first found a foreign body type of reaction in the nodules, we began to speculate as to what might have produced this reaction. Estrogens in oil have been known to do this; however, inquiry from the family doctor showed that both injections had been procaine penicillin G suspension. We next thought of a peculiar hypersensitive reaction to procaine itself. We had previously done several small surgical procedures on this patient under procaine, and no similar nodules had developed. To further test her we injected 3 cc. of 2% procaine solution deep in the subcutaneous fat. No similar nodules have resulted.

We found from several of the manufacturers that penicillin vials were coated with silicone, which was baked on so that the penicillin would not adhere to the walls of the vial. On inquiring from the Division of Industrial Medicine, University of Colorado School of Medicine, which has done extensive work in pulmonary silicosis, Dr. Bell informed us that only the silicate, such as silicon dioxide, in crystalline form would excite such a reaction and that the amorphous silicones would not produce any reaction in tissues. This belief has been supported by the work of several others. Helwig, Gardner, and Evans all support Dr. Bell's opinion. With this in mind, we investigated our sections under dark-field illumination for any crystalline structures, since Gardner had been able to demonstrate crystals in giant cells and necrobiotic areas. Thorough study of many sections showed no crystalline structures under either direct illumination or dark-field illumination.

At Dr. Weidman's suggestion, we swabbed the inside of a washed penicillin vial and examined the material under the dark-field microscope, with entirely negative results.

We believe that the wide scattering in the surrounding area can be satisfactorily explained on the basis of spread through the deep dermal lymphatics with the reaction developing at the site of deposit.

The sarcoid type of reaction that is seen so typically in our section has been described as a type of anergic response to the tubercle bacillus and also as a peculiar hypersensitive response

to other noxae such as beryllium and silica. Since we have been able to demonstrate no other agent present as being responsible for the reaction seen in our patient (whose history showed recurrence of an identical reaction on two widely separate occasions with different batches of procaine penicillin), we are driven to the conclusion that our patient presents a peculiar heretofore unreported reaction to penicillin.

SUMMARY

A new foreign body sarcoid-like structure deep in the skin is reported as a reaction to penicillin. Other possible etiologic factors we feel have been reasonably excluded.

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UNILATERAL HAIRY TONGUE

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The increased use of antibiotics during the past few years, especially in the form of troches and lozenges has once again focused attention on the phenomenon of hairy tongue. Ronchese and Kern recently reviewed the literature very completely. They reported a case of hairy tongue following the use of chlortetracycline (Aureomycin) ointment on the lips.

Unilateral hairy tongue.

The textbooks of dematology and articles agree on the general characteristics of this condition. At present two types of hairy tongue are recognized. The true is characterized by longer filaments and is believed to be a hereditary anomaly. The false is of much shorter duration and looked upon as secondary to some form of irritation. The conditions are described as black, brown, sepia, yellow, or even blue patches on the dorsum of the tongue and consist of filiform

projections of the papillae. They are usually situated in front of the "V" formed by the circumvallate papillae. Such lesions are located on the center of the tongue. By distribution and possible etiology the following case is of interest.

REPORT OF A CASE

History.—A 31-year-old white man (H. F.) presented himself to one of us (B. F.), on Dec. 11, 1951, complaining of a "bad taste" and a brown spot on one side of his tongue. The bad taste had been present for two days. On the second day, inspection revealed the brown discoloration of the left side of the tongue.

A careful review of the past history did not reveal the use of antibiotics during the preceding two months. No change in dentifrice or mouth wash was reported. The only significant item in the history was that two weeks prior to noticing this spot on his tongue, a left alveolar block was performed by a dentist.

Physical Examination.—On the dorsum of the tongue immediately to the left of the midline and extending almost from the tip to the base, there was brown discoloration. This, on closer inspection, consisted of many filamentous elongations of the papillae (Figure). Scraping and culture for yeast or fungi were negative. The condition cleared within two weeks on daily topical medication containing as the main ingredient zinc phenolsulfinate.

COMMENT

It would be of great interest if some definite physiological answer could be found to explain this unusual phenomenon of unilateral hairy tongue. Discussion with an exodontist (Dr. John Wynn) revealed that in most instances, because of the proximity of the inferior alveolar branch of the mandibular nerve to the lingual, the latter is equally affected by the introduction of the anesthetic. One may then postulate that the anesthetic and the presence of epinephrine (Adrenalin) leads to a local vasospasm, with consequent decreased functioning of the mucous and albuminous glands of the involved side of the tongue. This interference with the metabolism of the mucosa for some hours might initiate the changes reported here. Certainly the sharp delimitation must be explained on a neuroanatomic basis.

CONCLUSION

A case of unilateral hairy tongue is reported because of its distribution and the fact that it occurred on the same side of the tongue in which the patient had had an alveolar block performed two weeks prior to the onset of this condition.

Medical Arts Building.

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UNUSUAL SITE OF INFECTION WITH MICROSPORUM AUDOUINI

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AND
CLAIRE L. TASCHDJIAN, B.S.
NEW YORK

It is not surprising to find tinea circinata in one or several adult members of the families of children suffering from tinea capitis caused by the genus Microsporum. The following case is reported because of the unusual site of an infection with Microsporum audouini in an adolescent, presumably contracted from her young brother, who had tinea capitis.

From the Department of Dermatology and Syphilology, New York University Postgraduate School of Medicine (Dr. Marion B. Sulzberger, Chairman), and the Skin and Cancer Unit of the New York University Hospital.

REPORT OF CASE

D. M., a 17-year-old girl, was first seen by us on March 17, 1953. She presented circinate to imbricate lesions on the mons veneris. There were satellite lesions on the lower abdomen with a tendency to spread toward the right inguinal region (Figure). The disease was of three months' duration and had been unsuccessfully treated with various ointments.

Examination under filtered ultraviolet light revealed bright-green fluorescence of the pubic hair. The scalp, axillae, and the rest of the body were free of infection.

Microscopically, hairs from the pubic region showed typical ectothrix spore sheaths as well as extensive intrapilary involvement. Scales showed numerous filaments.

Circinate lesion due to Microsporum audouini involving the pubic area.

M. audouini was cultured from both hairs and scales on Sabouraud's agar and on rice medium.

The patient's 10-year-old brother had been first seen by us two months before, on Jan. 5, 1953, and presented a fluorescing tinea capitis of the occipital area. M. audouini was obtained in culture. The lesions continued to spread, and the child received x-ray epilation on Feb. 13. He was discharged as cured in April, 1953.

The patient's mother and 24-year-old brother were free of infection.

Between March and June the patient was seen at weekly intervals and treated with 5% ammoniated mercury and zincundesal (Salundek *) ointment. Despite treatment, the skin lesions continued to spread over the entire lower abdomen and throughout the inguinal regions. New

* Wallace & Tiernan Products, Inc., Belleville, N. J.

lesions appeared on the left flank and above both knees. The skin lesions subsided after three months, but fluorescence of the pubic hair, including the mons veneris and the labia majora, persisted.

COMMENT

Tinea capitis in adults is rare, but pubic involvement has to our knowledge never been reported. While both M. audouini and M. lanosum (canis) have been known to infect the eyelashes, eyebrows, and lanugo hair, an infection of the pubic area, such as described above, has never been observed by us among the many hundreds of cases of Microsporum infections which have passed through our clinic. Such an involvement is not mentioned in the standard textbooks.

SUMMARY

A case of infection of the pubic area with fluorescence due to Microsporum audouini is described in a 17-year-old girl whose brother suffered from tinea capitis caused by the same species of fungus.

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IMPROVED METHOD FOR PIERCING EARS

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Although the existing methods* for piercing ears are generally satisfactory, they have certain disadvantages which can, at times, complicate an otherwise simple procedure. The suture method, for example, which consists of placing sutures in the ear lobules, has the following drawbacks:

1. The suture tract frequently becomes secondarily infected and painful.

2. The sinus tract created is not always easily penerated by the earrings, and a false passage may occur.

3. The suture material must be worn for 7 to 10 days.

Seiger [2] and Kanee [3] recommend piercing the ear lobule from front to back with a 17- to 13-gauge hypodermic needle, the gauge to be determined by placing the barbed end of the earring in the lumina of various needles until a snug fit is obtained. The needle is thrust through the ear lobule into a piece of cork; the earring is inserted into the lumen, and firm continuous pres-

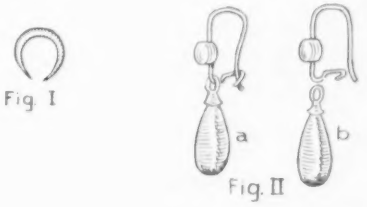
From the Department of Dermatology and Syphilology, The New York Medical College, Dr. Eugene F. Traub, Director.

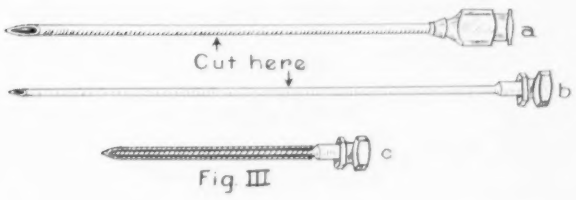
* References 1, 2 and 3.

sure is applied to convey it through the lobule as the needle is withdrawn. This method, though satisfactory when the earrings to be worn are identical back and front (Fig. I), is impractical for the placement of earrings which are not identical in this respect (Fig. II). The problem of how to place correctly earrings of the latter type has promoted the development of the following method for piercing ears.

METHOD

Preparation of Instruments.—The hubs are removed from 18 to 13-gauge hypodermic needles (Fig. III*a*). A stylet from an 18-gauge spinal needle is shortened from its distal end to exactly the same length as the hypodermic needle (Fig III*b*). The cut end of the stylet is then bevelled (Fig. III*c*).





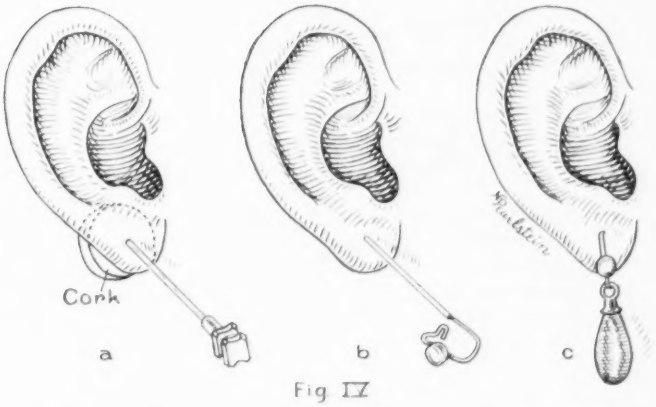


Fig. I.—Earring with identical anterior and posterior parts.

Fig. II.—Earrings with different anterior and posterior parts.

Fig. III.—(*a*) Needle (intramuscular); (*b*) spinal needle stylet; (*c*) spinal needle stylet in position inside intramuscular needle.

Fig. IV.—Method of insertion of earring.

Procedure.—The barbed-end of the earring is inserted into the lumina of the various hypodermic needles in order to determine the gauge of the earring. The stylet is placed inside the needle affording the closest fit, care being taken to keep the bevels in parallel planes. The exact spot to be pierced is indicated by the patient, the lobule is cleansed with thimersol (merthiolate)

and alcohol, and the needle and stylet together are thrust through from the front into a piece of cork held behind the ear lobule (Fig. IV*a*). The stylet is then removed and the barbed-end of the earring is inserted into the anterior lumen of the needle (Fig. IV*b*). Gentle pressure is applied to the earring and needle, conveying both through the lobule (Fig. IV*c*). Bacitracin ointment (Baciguent) is applied to the area surrounding the newly created tract. Since the procedure is rapid and as the ear lobule has a high threshold for pain, anesthesia is unnecessary.

SUMMARY

An improved method for piercing ears is described.

898 Park Avenue.

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CONTACT DERMATITIS FROM CHLORCYCLIZINE HYDROCHLORIDE (PERAZIL) CREAM

Report of Four Cases

SAMUEL AYRES III, M.D.
AND
SAMUEL AYRES Jr., M.D.
LOS ANGELES

In a previous report by us on the use of 1% chlorcyclizine hydrochloride in a greaselesss ointment base (Perazil cream, Burroughs Wellcome & Company, Inc.) for the relief of pruritus, it was stated that at that time no cases of contact sensitization from its use had been observed by us, although the preparation had been used in several hundred cases over a period of more than a year.

It was further stated that as the use of this preparation increased, it was to be expected that a certain incidence of sensitization would become evident, but that it would be significantly lower than in the case of the other antihistaminic drugs which have been made available for topical application.

Since that report, we have used 1% chlorcyclizine hydrochloride ointment in many hundred additional patients. Its over-all effectiveness as an antipruritic and the high degree of tolerance to it have made it a very useful preparation.

Four cases of contact sensitization from the chlorcyclizine ointment used topically have been seen by us in recent months, and to our knowledge there have been no previous reports of contact sensitization to this drug.

REPORT OF CASES

Case 1.—J. S., 24, was seen on Aug. 21, 1952, with a subacute eczematous eruption of the hands and forearms of two months' duration. She had used chlorcyclizine ointment prescribed by another doctor for about one month, with temporary benefit. A patch test to chlorcyclizine ointment elicited a 4+ reaction, whereas the ointment base without chlorcyclizine gave no reaction.

Case 2.—M. B., 31, was seen on Jan. 16, 1953, with an acute vesicular eruption of two fingers of one week's duration and an erythematous eruption of the face of one day's duration. She had been using tripelennamine (Pyribenzamine) cream. A delayed 4+ patch test reaction to chlorcyclizine ointment was obtained, coincident with a severe flare-up. Subsequently two repeated patch tests gave 3+ results, with negative ointment base controls. A 4+ reaction to tripelennamine cream was also obtained. She had not used chlorcyclizine cream, but chlorcyclizine was given orally just prior to the exacerbation of the eruption.

CASE 3.—F. T., 56, was first seen in August, 1952, with a localized neurodermatitis in the left crural area, for which chlorcyclizine ointment was prescribed. She used it intermittently until Feb. 24, 1953, at which time she was instructed to use it more frequently because of increased pruritis. She returned on March 10 with an acute dermatitis in this area, and she subsequently developed an allergic flare on the forearms and chest. A patch test to chlorcyclizine ointment revealed a 4+ reaction with a negative reaction to the base alone. After the acute eruption had subsided, a repeat patch test gave a persistent 2+ reaction to chlorcyclizine ointment, with a negative ointment base control.

CASE 4.—E. I., 63, was seen on April 17, 1953, with a pruritic, erythematous eruption of the face of four weeks' duration. She had been seen by us in July, 1951, for a similar eruption found by patch test to be due to two of her cosmetics. At that time chlorcyclizine ointment was dispensed, which she used about 11 days. For the present eruption she had used the same chlorcyclizine ointment previously dispensed. A patch test to chlorcyclizine ointment revealed a slight reaction at 48 hours, with a 2 to 3+ delayed reaction, while the ointment base alone gave a negative reaction.

SUMMARY AND CONCLUSIONS

These four instances of contact sensitization to chlorcyclizine hydrochloride ointment as proved by patch test were the only cases seen thus far in its extensive use over a period of about three years in many hundreds of cases. Thus, our earlier impression that the incidence of sensitization would be low apparently has been borne out by subsequent experience, and at the present writing the incidence is sufficiently low that we do not consider that it constitutes an objection to its use, although the possibility of sensitization should be kept in mind.

2007 Wilshire Blvd.

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Society Transactions

METROPOLITAN DERMATOLOGICAL SOCIETY OF LOS ANGELES

Stanton B. May, M.D., *President*

Fred F. Feldman, M.D., *Vice-President*

Irving A. Lewe, M.D., *Secretary*

Nov. 24, 1953

Chronic Porphyria (Porphyria Hepatica, Mixed or "Cutanea Tarda" Type); Bullosis Actinica et Mechanica, Hydroa Vacciniforme. Presented by DR. MURRAY ZIMMERMAN.

A 52-year-old house painter was in good health until 1933, when he developed a peculiar dark gray tan on sun-exposed areas. This continued until 1947, when he began to develop blisters and crusted lesions on sun-exposed areas, which healed leaving severe pitted scars. In 1951, the patient noticed that if he had to hold his urine for a long time, it showed a reddish discoloration, and he also noticed accidentally that a urine specimen left for 24 hours darkened considerably to a reddish color. He states that there has been no discomfort except that about two hours after painting on the sunny side of a house he has noticed itching and burning on sun-exposed areas. He has developed painless blisters on his hands, which heal slowly with crust formation after exposure to paint thinner. All symptoms stopped from 1936 until 1945, when he had an indoor job as a custodian. During these years even exposure to intense sunlight (while fishing on his day off) had no significant effect. About one year after he went back to painting, in 1946, symptoms began again. There is no significant drug history.

This patient had one acute episode of gastrointestinal colic, which he ascribed to painter's colic in 1929. He states that in his early years he drank up to a pint of whiskey a week but that for many years he has drunk nothing but beer, averaging about three cans a week. He had scarlet fever at the age of 10, pneumonia at 15, and gonococcal urethritis at 24, clearing without further difficulty. He states that he has not had chancre or syphilis infection, jaundice, gall bladder symptoms, or digestive disturbances other than mild indigestion from eating cabbage. He was severely burned on the lower extremities with kerosene during childhood. His burn scar, on the right posterior thigh, broke down about one year ago and has been ulcerated ever since.

No other family member has ever had skin trouble, photosensitivity, or discolored urine.

Examination of the skin revealed multiple scaling and pustular depigmented and hyperpigmented ostraceous lesions on the face, neck, and hands; multiple small (up to 1 cm. in diameter) tense bullae on the hands with no peripheral inflammation; severe pitted scarring of the face, neck, and scalp. The skin on the face, neck, chest, and shoulders exhibits a distinctive grayish pigmentation and a slightly glazed appearance on the chest and shoulders. There is a 7-cm.-diameter ulcer on the right posterior thigh in the old atrophic scar tissue, which extends from the buttocks downward, over both lower extremities posteriorly.

Laboratory examinations revealed the following data: serologic tests for syphilis: VDRL, positive; Kahn 4+. There was no sugar, albumin, or significant microscopic findings in the urine. The urine fluoresces bright pink under Wood's light. The urine which has been acidified to convert other fluorescent materials still flouresces pink. After acidification with acetic acid and washing with ether (to remove coproporphyrins) the same bright fluorescence persists, showing that the fluorescent substance in the urine is uroporphyrin. Total porphyrins: 11,000 mg. of coproporphyrin and 15,600 mg. of uroporphyrin in the 24-hour urine specimen. The patient's teeth exhibit a pinkish flourescence on Wood's light examination.

Light tests revealed that normal erythema developed after exposure to 2,537, 2,967, 25 and 29 A. mixed. No erythema developed after five minutes of exposure to 3,660 A., and no erythema developed where wave lengths shorter than 3,100 A. were filtered out by glass. No evidence of photosensitivity developed in the skin of Dr. Zimmerman where patient's serum was injected after exposure to 2,500 or 2,900 A. wave lengths. Blood studies:

RBC: 4,490,000 cells per cubic millimeter
Hgb.: 98%, 16.7 gm.
Color index: 0.90.
WBC: 7,000 cells per cubic millimeter
Differential: 71% segmented
1% eosinophiles
19% lymphocytes
9% monocytes
Stained smear appears normal.
No basophilic stippling.

Liver Function Tests: Icterus index, 8.
Thymol turbidity, 9 units.
Sulfobromophthalein test, 5.3% dye retention at end of 45 minutes.

On Nov. 13, the patient was started on 600,000 units of penicillin every two days, nicotinic acid 100 mg. three times daily, orally, and crude liver, vitamin B complex, and Vitamin B_{12} three times weekly. His response to therapy has been excellent from the first.

Biopsy specimens were taken from many sites, including both "normal" and "abnormal" tissue samples. The slides are presented.

DISCUSSION

DR. ARTHUR FLETCHER HALL: I did not see in the history that this man had any systemic symptoms of porphyria; this is of interest.

DR. CHARLES SHERTER: This is an interesting case. Apparently this type of porphyria with bullous manifestations of the skin is often associated with liver disease, secondary to chronic alcoholism. Several factors all working together are required in the formation of the bullae; namely, the porphyric state, trauma, and sunlight. Interestingly enough, it is not possible to reproduce the picture on a laboratory basis using utraviolet light and induced trauma. Certainly, if one is dealing with a patient who has a bullous eruption of unknown origin, especially with a history of chronic alcoholism and/or liver disease, it behooves the dermatologist to check for uroporphyrins. The fact that a simple test using the Wood's light on freshly voided urine is readily available should bring the diagnosis of this relatively rare disease within the realm of office procedure.

DR. ARTHUR FLETCHER HALL: I should like to suggest that in an effort to control the bulla formation of this man, which is really the basis of his skin trouble, he be given sodium citrate in rather large doses. I have had two cases in which porphyria was not investigated but in which the bullae were produced by exhibition of sunlight and trauma; these were controlled completely by sodium citrate. I think it will be very interesting to see whether this man develops skin cancer. I feel that the wave lengths of light which are carcinogenic are probably different from those which tend to aggravate lupus erythematosus and possibly other systemic states, such as porphyria. At the last meeting of the Los Angeles Dermatological Society, by a strange coincidence, a case very similar to this was presented with the diagnosis of lupus erythematosus with porphyria. This man had systemic symptoms of porphyria and lesions very closely mimicking disseminated discoid lupus erythematosus. I felt there were areas in tonight's patient, particularly in the scalp, that suggested discoid lupus erythematosus. I don't know whether this man would be more susceptible to skin cancer or not; it would be very interesting to take a biopsy specimen from any lesions that were suspected of malignancy. The back of the hand was more or less ulcerated and suggested the possibility of carcinoma. What did the biopsy show on that?

DR. MURRAY ZIMMERMAN: That lesion simulated a squamous cell carcinoma so closely that I told him I believed he had a squamous cell carcinoma. On it, he had a crust about ¾ in. (1.9. cm.) high. None of his lesions showed evidence of basophilic degeneration, metachromasia, or other light-induced changes, much less any sign of precancerous change. Clinically, I thought them cancerous.

DR. HAROLD PRICE: One of the newer tests for the diagnosis of lead poisoning is the increase in the coproporphyrin in the serum and in the urine. Is there a suspicion that there may be lead poisoning in this case? Inasmuch as there was an increase in the coproporphyrin in the urine, a further study should be made to find out whether the patient does have a high level of lead in his serum and urine. I should like to mention a new treatment for lead poisoning which I think will interest dermatologists because it consists of mobilization of lead from the tissues and removing it through the use of a chelating agent known as EDTA (ethylenediaminetetraacetic acid). There are some studies going on now to determine whether the same agent can be utilized for the mobilization of other heavy metals, such as gold or arsenic.

DR. JOSEPH R. TRAUB: What dosage of sodium citrate do you suggest?

DR. ARTHUR FLETCHER HALL: Thirty grains (1.9 gm.), t.i.d.

DR. MURRAY ZIMMERMAN: Dr. Price commented on lead poisoning as a cause of porphyria. This is a possibility which I also suspected and asked to have the red cells checked for stippling. This does not exist. Toxicity from many substances will give an increased porphyrin level in the urine. Lead, methyl chloride, arsenic, and many other toxins will depress the bone marrow, will raise the coproporphyrin level from what is normal (60 to 208 γ for 24 hours) to 100 to 4,000 γ. This test has been suggested by Watson as a sensitivity index of whether industrial workers are being overexposed to toxic compounds. This patient has porphyria of cutanea tarda type, rather than a lead poisoning, which one would expect to be more acute.

The action and absorption spectra of the porphyrins are around 5,400 A. I think that explains why this patient shows no histologic evidence of sunlight degeneration on exposed skin. The carcinogenic and senile-elastosis-producing wave lengths are clustered around 2,967 A., the absorption action spectrum of cytoplasm. This patient had had no abnormal reaction either to 2,537 A., 2,967 A., or 3,660 A. I injected the serum into my forearm skin, and after exposure to 2,537, 2,967, and 3,660 A., no evidence of photosensitivity developed.

Case for Diagnosis: Necrobiosis Lipoidica. Presented by DR. MEYER BERKE.

A 33-year-old white woman first noticed in 1949 the appearance of brownish, smooth, telangiectatic, oval plaques on both tibial surfaces, which have gradually enlarged in size. The patient's health has been good. A hysterectomy was done in 1946. Her grandmother is the only member of the family having had diabetes.

A biopsy specimen was removed. The glucose tolerance test showed a normal curve. Urinalysis was normal.

Treatment has consisted of mixed tocopherols orally and the use of hydrocortisone ointment. Despite treatment, there has been some increase in the size of the lesions.

DISCUSSION

MARGARET ANN STORKAN, M.D.: (Comments-Slide)

DR. FRED F. FELDMAN: We have not had an opportunity to treat a patient with necrobiosis lipoidica diabeticorum since hydrocortisone (Compound F) ointment has become available. Our experience in this condition with cortisone (Compound E) ointment has been good. Most of the patients have shown varying degrees of improvement. Our best results occurred in three patients who had ulcers in the plaques of necrobiosis, suggesting that better absorption of the active agent occurred. At best, the penetration of cortisone in ointment form into such thick plaques cannot be too efficient. Therefore, I suggest that cortisone in a concentration of 25 mg. per gram of base be used for one to two months for proper evaluation. It should be massaged diligently into the affected areas at least three or four times daily. The ineffectiveness of topical cortisone in the patient presented tonight may be due to the fact that she applied the medication improperly. Upon questioning, the patient mentioned that on some days she used the ointment sparingly, and on other days she omitted it completely.

I should like to ask Dr. Price whether any results were produced when cortisone ointment was used properly on his patient.

DR. HAROLD PRICE, M.D.: The answer is no, and I think the patient was faithful in using the ointment. I did not notice any particular change. I might mention one therapy I did use in this patient. One of the characteristics of the lesions was that the borders were slightly elevated, and there was a tendency toward peripheral extension. I used solid carbon dioxide on the periphery, with fairly firm pressure, and the lesion did flatten down.

DR. CHARLES SHERTER: I should like to suggest the use of hydrocortisone intradermally and/or subcutaneously into the lesions.

Perhaps this is a localized vascular allergy with a very mild polyarteritis reaction, and cortisone would be of help.

DR. LEONARD E. SAVITT: I treated a patient with necrobiosis lipoidica diabeticorum of two years' standing, using solid carbon dioxide. It was neither helpful nor harmful. Later I applied cortisone ointment made up according to the directions of Dr. Newman (a solution of cortisone was filtered and the residue mixed with a soluble base). The lesions cleared almost completely in a few weeks.

Lymphoma (Reticulum Cell Sarcoma). Presented by DR. CHESTER M. SIDELL.

Alopecia Areata Totalis. Presented by DR. STANTON B. MAY.

Lichen Sclerosis et Atrophicus, Vulvae. Presented by DR. MURRAY ZIMMERMAN.

Facial Hemiatrophy? Early in Coup de Sabre Scleroderma. Presented by DR. MURRAY ZIMMERMAN for diagnosis and suggestions for treatment.

Polyneuritic Leprosy. Presented by DR. STANTON B. MAY.

Scleroderma? Lichen Sclerosus et Atrophicus? Presented by DR. IRVING A. LEWE for diagnosis.

Balanitis Xerotica Obliterans. Presented by DR. IRVING A. LEWE.

Acrodermatitis Continua? Psoriasis with Pustules and Arthritis? Presented by DR. MEYER BERKE for diagnosis.

Facial Granuloma with Eosinophilia: Recalcitrant Hyperkeratotic Dermatitis of Hands. Presented by DR. LAURENCE J. UNDERWOOD and DR. WALTER S. GREEN.

Nevus Comedonicus Unilateralis. Presented by DR. STANTON B. MAY for therapeutic suggestions.

Lichen Planus Generalized. Presented by DR. SIDNEY J. ROSE for therapeutic suggestions.

Psoriasis—Nails. Presented by DR. LAURENCE J. UNDERWOOD and DR. WALTER S. GREEN.

Sebaceous Adenoma? Sarcoid? Presented by DR. JOHN W. CARNEY for diagnosis.

NEW YORK ACADEMY OF MEDICINE, SECTION OF DERMATOLOGY AND SYPHILOLOGY

J. Lowry Miller, M.D., *Chairman*

Timothy J. Riordan, M.D., *Secretary*

Oct. 6, 1953

All the cases presented at this meeting were from New York Hospital.

Incontinentia Pigmenti. Presented by DR. GEORGE M. LEWIS for DR. JEAN CRAMER.

History.—D. M., a white male infant, was born in Astoria General Hospital, June 5, 1953, and on the first day of life was noted to have an eruption on the face and extremities. This faded by the second day save for soles and fingers. On the fourth day diffuse, dusky-gray pigmentation of entire integument was noted, without respiratory distress, and the child was transferred to New York Hospital. The antepartum course and labor were uneventful, with no history of medication or viral infection during the last trimester. The family history is negative.

Examination.—6/9/53.—Epidermis generally dusky-gray in color. Clustered firm-walled vesicles and crusted papules, ranging from 0.1 to 1 cm. in diameter, were arranged in linear fashion on the posterior aspects of the legs, flexor aspects of the arms, on soles and palms, and scattered over the trunk and scalp.

6/11/53. Normal hue of integument.

7/11/53. Warty papular lesions noted on left middle finger and dorsa of feet.

9/11/53. Areas of atrophy, depressed depigmented scarring, and minimal pigmentation noted on legs in sites of previous involvement. Warty and vesicular elements gone.

Laboratory Findings.—Hemogram, 6/10/53:

Hgb	19.6 gm. per 100 cu. cc.	Lymph.	60%
RBC	4,500,000	Mono.	2%
WBC	10,700	Eos.	3%
		Baso.	0
		PMN	27% mature 4% bands

Wassermann: negative

Urinalysis: normal

Cholesterol, protein: within normal

X-rays, chest and long bones: negative

Angle of left acetabulum is 30 degrees as compared to right acetabulum angle of 20 degrees.

Circulating eosinophile count: 1,900 per cu. cm.

Viral studies: negative

Biopsy.—A thin layer of hyperkeratosis overlies the intact epidermis, which contains three large intraepidermal vesicles. The vesicles are filled with eosinophiles and a few lymphocytes, and some spongiosis and washing-out of the basal cell margin together with inflammatory cell infiltration of the lower epidermis are noted. The cutis is quite edematous and infiltrated with many eosinophiles and some round cells. The blood vessels are dilated, particularly in relation to the inflammatory reaction, with some concentration of the infiltrate in perivascular areas. The collagen is distorted in this area. Several immature hair follicles are noted. Diagnosis: Vesicular stage of incontinentia pigmenti in newborn skin.

Course.—The infant was treated for acquired methemoglobinemia with methylene blue, with rapid disappearance of abnormal skin color and reversal of blood to normal. The probable congenital dysplasia of the left hip is being carefully observed with frequent x-rays. No vesicular or warty skin lesions noted now.

DISCUSSION

Dr. Helen Curth: I believe we have progressed considerably if we can make a diagnosis of incontinentia pigmenti when we cannot see any lesions or any evidence of them histologically. I believe, however, that it is entirely possible that this child will develop incontinentia pigmenti, and at any rate this case belongs to that group which Carney described so well. A few features of this syndrome seem characteristic. These are the verrucous lesions, their distribution, and the subsequent atrophy. The child also has chondrodysplasia of the left hip. This may be the result of chondrodysplasia calcificans congenita, which was present in some of my cases. The fact that the child is a boy does not speak against the diagnosis of incontinentia pigmenti because about 4 cases in boys have been seen among the 60 or 70 cases described. I have, however, never heard of methemoglobinemia from which this child suffered the first days after birth.

Dr. Marion B. Sulzberger: I fully agree with the presentation and with what Dr. Curth has just said. I should just like to emphasize that at present I see nothing characteristic of incontinentia pigmenti so far as the cutaneous manifestations of this case are concerned, either clinically or in the biopsy report. Therefore, I think that one would be wise to insert a question mark after the diagnosis, at least until the characteristic skin lesions appear, if they will appear. But the other manifestations in this patient (with the exception of the methemoglobinemia) are certainly those which have in some cases been described as associated with the typical skin lesions of incontinentia pigmenti.

Dr. David Bloom: The pigmentation in this child in the first few months of life was much more extensive and has receded since then to the present small extent. This is a common occurrence in incontinentia pigmenti.

Dr. George M. Lewis: It has been our good fortune to study three cases which were considered to belong in this syndrome. Since the publication of Carney's article, we have been more aware of the early vesicular lesions.

Dr. Jean Cramer: As Dr. Lewis said, we were unusually fortunate in having two cases of incontinentia pigmenti within the period of a year at the New York Hospital. The first was born in the New York Hospital and the day after birth was noted to have what the

pediatricians called "impetigo," and a dermatology consultant was called. We observed the case closely and over a period of a few days watched her develop quite typical linear patches of vesicles, as this baby did. However, her eruption was more extensive, involving the extensor aspects of arms, fingers and legs and the palms and soles, with typical clustered lesions on the trunk. The vesicular stage persisted for about two or three months and was not followed by the verrucous stage but progressed directly into the pigmentary stage. She has the classic pigmentary changes at present, with associated delayed dentition. At the age of 18 months she has only two teeth but otherwise seems to be of normal skeletal and mental development. The very high circulating eosinophile count seen in the first case was duplicated in this baby. Viral studies of the vesicular fluid from the infant presented tonight were done to rule out the remote possibility that this syndrome might represent a viral infection in the early months in utero. The results were not too satisfactory. Nothing was grown out after a period of two months, but the amount of fluid obtained was not adequate for studies.

Case for Diagnosis: Riehl's Melanosis? Poikiloderma Reticulare (Civatte)? Post-dermatitic Pigmentation? Presented by DR. ANTHONY C. CIPOLLARO for DR. WORTHINGTON.

History.—P. G., a 47-year-old Puerto Rican woman, in the United States for the past 14 years, has noted, over the past 5 years, the gradual development of brownish-black, lacy pigmentation on the neck, then the breasts, arms, and shoulders. This has been asymptomatic, and she gives no history of any previous dermatitis in these or any other areas.

Past history includes no serious illnesses, no family history of similar skin lesions.

Examination.—There is a fine, reticulated, blackish-brown, macular pigmentation over the anterior neck, both breasts, the scapular areas, and the arms. The skin is not thickened or atrophic, but is abnormally dry.

Laboratory Findings.—Mazzini serologic test: negative

Biopsy: The epidermis shows irregular thinning. A mild basket-weave hyperkeratosis is found in areas, with increased hydropic changes in the epidermis, chiefly in the basal margin. One small portion of the basal layer shows disorganization (probably artefact). The basal layer shows no abnormal increase in melanin. The papillary and subpapillary layer of the corium show irregular heavy deposits of melanin both within and outside the chromatophores. There is a spotty lymphocytic, perivascular infiltrate, with no marked dilation or thickening of the vessels.

Impression: Consistent with Riehl's melanosis or poikiloderma reticulare (Civatte). Post dermatitis pigmentation not ruled out.

DISCUSSION

DR. JUAN LARRALDE: Frankly, I don't see any definite features of melanosis there. This woman is a Latin-American mulatto, and it is not uncommon to find that type of hyperpigmentation in those people.

DR. DOUGLAS P. TORRE: I should like to know whether Dr. Larralde observed it in young people. This patient definitely noted the onset a few years ago, in middle age. I wonder whether this is a pigmentation from birth or from later on.

DR. JUAN LARRALDE: The patients that I have seen have been adults.

DR. MAURICE J. COSTELLO: I thought that this case resembled to some extent an abortive type of pseudoacanthosis nigricans. There is some suggestion of thickening of the skin on the neck. I think the type of pigmentation that occurs in mulattoes is reticulate in type, especially on the face. I have seen many examples in Bellevue Hospital. I have never seen anything just like this before.

DR. HELEN CURTH: I saw the patient's arms only. There she showed reticulated pigmentation. That would not fit in with pseudoacanthosis nigricans.

DR. BEATRICE M. KESTEN: My impression of Riehl's melanosis was that after the First World War Riehl presented a group of patients who had bronzed pigmentation chiefly on areas exposed to sun. I think he felt it might have been due to a very poor, largely carbohydrate

diet. Since that time I know the term has been bandied about and sometimes confused with melanosis due to photosensitization with coal tar products. As to what this woman has, I don't know, but I am of the impression—and I agree with the first speaker—that this is not uncommon in adults of mixed races.

DR. JACK WOLF: I cannot offer a diagnosis in this case. The eruption over the breasts is not a pigmentary disturbance. On examination, my impression was that the eruption over the breasts was purely vascular. Histological examination of tissue from this location may be helpful in arriving at a diagnosis and in confirming the impression that we are dealing with poikiloderma vascularis atrophicans.

DR. ANTHONY C. CIPOLLARO: We studied this patient thoroughly at the New York Hospital; we presented her at several of our conferences; we have done several biopsies, and we have had an opportunity of discussing the fine clinical points that have been brought out tonight, and yet we are unable to arrive at a definite diagnosis. Our histologic studies indicated that Riehl's melanosis is to be considered, and there were changes which also indicated the possibility of poikiloderma reticulare. The lesions on the chest and on the breasts clinically appeared to be vascular rather than pigmentary. We really have no definite diagnosis to offer.

Lipid Dystrophy (Type?). Presented by DR. JOHN W. DOUGHERTY for DR. JEAN CRAMER.

History.—N. D., the product of a normal pregnancy, was in good health until 11 months ago, when an erythematous, blotchy, macular eruption was noted on exposed areas, with mild puffiness of hands, feet, and face. This was treated as an atopic dermatitis without improvement. About eight months ago the child became somewhat irritable and slept more than usual. Six months ago, corneal ulcerations developed, with subsequent scarring, despite use of cortisone ointment and other medicaments.

Family history: negative.

Physical Examination.—Skin: generalized blotchy, faint macular erythema, most marked on hands, feet, and face. Blanching noted on diascopic pressure, with telangiectasia on face. Suggestion of areas of macular atrophy alternating with areas of brownish macular pigmentation on extremities, including palms and soles.

Hands, wrists, fingers, legs, and feet appear wide, short, and puffy, particularly about proximal phanlanges and over dorsa of hands and feet.

Eyes: clouding of corneas with bilateral ulcerations. Pupils irregular and respond poorly to light. Fundi: many posterior synechiae. Many large white keratic precipitates, cloudiness of the anterior chamber, and occasional cells. Retrolental membrane present.

Nodes: shotty cervical and inguinal nodes.

Abdomen: liver enlarged 2 fingerbreadths below the costal margin.

Laboratory Findings.—Negative findings: routine urinalysis, urine for porphyrins, and mercury; tuberculin, histoplasmin, and Kveim skin tests. WBC, 15,600, with differential showing slight shift to left; Hgb, RBC, normal. Normal: vitamin A tolerance, glucose tolerance, protein-bound iodine, spinal fluid, ESR, BUN, sugar, CO_2 Cl, Na, bilirubin, protein, and A/G ratio, Thorne test.

X-rays: normal skull IUP. Flat plate of abdomen showed moderate hepatosplenomegaly. Chest plate: infiltration of right lower lobe, which resolved slightly during hospitalization.

Bone marrow: normal save for slight increase in plasma cells.

Excision biopsy of cervical and axillary lymph nodes: pathological diagnosis—chronic granulomatous process.

Excision of mass, right wrist: pathological diagnosis—chronic granulomatous inflammatory process.

Excision of hemangioma, right frontal area: pathological diagnosis—capillary hemangioma, chronic granulomatous inflammatory process.

Note: von Kossa, Gram, acid-fast, and Sudan stains—negative.

Biopsies, left buttock, left arm, showed similar pictures. The epidermis shows a normal granular layer and slight hyperkeratosis. The Malpighian and basal layers are intact. In the subpapillary layer, focal collections of reticuloendothelial proliferation are present, which include

giant cells of the foreign-body type, often showing a foamy cytoplasm and vacuoles. Many of these collections extend deep into the corium, especially about the hair follicles. Many of the giant cells are huge and contain numerous vesicular nuclei in a cluster. A few lymphocytes are present in the granulomatous foci. The blood vessels seem normal.

Course.—The patient has continued about the same, with poor appetite. Ophthalmology consultants' impressions were keratitis of unknown type; anterior uveitis; retrolental membrane of unknown type. No definite systemic diagnosis was arrived at, and patient is thought to have a lipid disorder of an unknown type.

At present can stand and sit well, says some words, but shows no evidence of residual vision.

DISCUSSION

DR. JOHN W. DOUGHERTY: I should like to ask Dr. Helen Curth if the skin lesions here resemble in any way those that she described in the patient with follicular atrophoderma.

DR. HELEN CURTH: They do not resemble follicular atrophoderma. The condition in the case presented tonight shows an inflammatory process, while follicular atrophoderma is the end stage of a process with dimples at the site of follicles.

DR. DAVID BLOOM: I should like to know if any fat stains have been made.

DR. JOHN W. DOUGHERTY: Yes, they are negative.

DR. JOSE MAY, Montevideo, Uruguay: I have never seen a case like this. I should like to know whether the Rh factor in the parents has been studied.

DR. JEAN CRAMER: I don't believe that has been studied.

DR. ARTHUR W. GRACE: I was interested to hear that the fat stains were done on the tissue and no fat-positive material apparently was found. I think it is difficult to make a diagnosis without finding some material that took up the fat stain.

DR. JOHN W. DOUGHERTY: In answer to Dr. Grace, the only justification we had for the diagnosis of lipoidosis was the foam cells. The final conclusion we have come to is it is somewhere in the lipodystrophy field. It is not much of a conclusion after an ophthalmologist, a pediatrician, and a man with an ultracentrifuge worked over this patient.

Primordial Dwarfism; Discoid Lupus Erythematosus. Presented by DR. DOUGLAS P. TORRE for DR. JEAN CRAMER.

History.—S. B., aged 2½ years, the product of a normal gestation, was noted to be small at birth, and at 6 months weighed only 7 lb. 7 oz. (3,375 gm.). Studies done at Mt. Sinai Hospital resulted in the diagnosis of primordial dwarfism. At 10 months of age, following a one-month course of ultraviolet treatments, an erythematous, slightly scaly eruption appeared in butterfly area of cheeks, lips, and eyelids. Weekly injections of bismuth caused no improvement. She was admitted to the New York Hospital Sept. 30, 1952, for the excision of a supernumerary phalanx of the left thumb and evaluation of endocrine status. Studies for evaluation of the child's retarded growth included measurements which proved the child to be of normal proportion for her age, with no evidence of hypothyroidism. The final diagnosis was primordial dwarfism.

Examination.—A tiny but well-proportioned girl, very slender, weight 15 kg. Skin: Over butterfly area, chin, right eyelid, and lips scattered erythematous, macular, slightly scaly lesions are seen. Similar blotchy lesions are noted on extensor aspect of arms.

Laboratory Findings.—Cholesterol, creatine excretion, urinary 17-ketosteroids, glucose tolerance, corticotropin (ACTH) tolerance, insulin tolerance, psychometrics, urine, liver function tests, chest x-rays, bone marrow, calcium, phosphorus, phosphatase, BUN: in normal range.

L. E. cell and urinary porphyrins: negative. Hgb: 10.5 gm.; WBC: 9,040; RBC: 3,500,000; differential: normal.

Biopsy: refused.

Course.—Quinacrine (Atabrine) therapy was attempted, but patient refused to take the medication despite trials with elixir, crushed tablet, and rectal instillation. Finally, sugar-coated tablets of 0.1 gm. each, daily for 12 days, were taken, with prompt development of intense icterus and fading of the lesions. Following cessation of treatment and sun exposure, new areas of

scaling and erythema developed on arms, where the patient had been exposed without benefit of sunscreen. Liver and vitamin B_{12} injections, and a trial of hydrocortisone (Hydrocortone) ointment applied locally, have resulted in no improvement.

DISCUSSION

DR. DAVID BLOOM: This is the third such case I have seen. One was presented from the Vanderbilt Clinic by Dr. Machacek in March, 1953. At that time I mentioned that we had such a case under observation since 1941 at the Skin and Cancer Unit. These three cases are pituitary dwarfs. One feature which makes them look very much alike is the precocious senile appearance of the face. In addition, all three of them show erythematous spots on the face, which at first glance appear as lupus erythematosus. But after long observation of our patient and after a pathologic examination we came to the conclusion that this erythema may be designated as congenital telangiectasia. Our patient shows also another congenital abnormality, namely, ichthyosis-hystrix-like eruption on the trunk. Like the patient presented tonight, our patient shows lesions on the lips which are markedly exacerbated in the summer and consist of bullae and crusted lesions. Uroporphyrin was not found in our patient, and we believe that this bullous eruption is due to sun sensitivity. The occurrence of such a combination of symptoms in three persons justifies the assumption that we are dealing with a congenital syndrome entity.

DR. FRANK E. CORMIA: I was quite interested in Dr. Bloom's remarks. I had the impression that, while the eruption resembled lupus erythematosus, yet there was something not quite right about it. I believe that what he has pointed out is probably the true explanation. She has the peculiar lability of blood vessels which may be inherited in this condition. I think it is of further interest that she has not responded up to date to standard treatment. At the present time she is receiving liver extract and vitamin B_{12}. She has had some quinacrine. The condition is now more extensive than at the onset of therapy. I think that the syndrome as presented is similar to the entity described by Dr. Bloom.

DR. HELEN CURTH: In the discussion last year I mentioned a fourth case, that of a little girl who is now under the care of Dr. Mintzer. All the children I have seen were of Jewish parentage. I believe it is also important to bring out that these children seem to have normal siblings. The child shown tonight has a normal younger sister or brother. The child I saw had five or six normal brothers or sisters. The parents of the child presented here last year were encouraged by these reports and are now expecting another child. From a genetic point of view the isolated occurrence of the disorder in a family is important.

DR. IDA J. MINTZER: In the case that Dr. Curth is referring to, the child actually never had distinct lesions of lupus erythematosus, but she does get episodes of erythema over the flush areas of the face.

I have another patient that I have been observing for the last five and a half years. The child is now 6 years old and, when he first came under my surveillance, I made a tentative diagnosis of Stevens-Johnson disease, on the basis of the bullous lesions, erosions, and crusting of the lips and mucous membrane of the mouth, the genitalia, and the eyelids. Subsequently the child developed similar lesions on the dorsa of the hands and flush areas of the face. Lupus erythematosus was strongly suspected at this time, and a biopsy was done by Dr. Sachs, who confirmed the suspicion of lupus erythematosus. During the course of further observation of this child, we have noted repeated episodes of exacerbation along with periods of remission.

The patient responds very well to small doses of quinacrine and supportive therapy.

DR. JOSE MAY, Montevideo, Uruguay: I should like to ask the question I asked before, that is, if the Rh factor has also been studied. I do not believe the diagnosis of lupus erythematosus is correct. The reason for which I would like to know whether the Rh factor has been studied is that this child had the appearance called *chétif* by the French authors, which can be seen in children of syphilitic parents. The Rh factor is capable, in my experience, of producing dystrophy of this type.

DR. GEORGE M. LEWIS: The clinical features are those of lupus erythematosus, including the presence of atrophy. The lesions here are not telangiectatic, as in at least one of the other cases of similar type. Unfortunately, the parents refuse to allow a biopsy. Perhaps this is a new entity. However, the evidence at hand is more in favor of lupus erythematosus.

DR. DOUGLAS P. TORRE: There is no Rh incompatability. This patient did respond somewhat to quinacrine, but that would not solve the problem whether this is a lupus-erythematosus-like syndrome or whether it is true lupus erythematosus, because quinacrine in pigmenting the skin cuts down the sun sensitivity. This patient is sun sensitive. The yellowing is a nonspecific effect. It should give some improvement. This is not true lupus erythematosus. It should not respond to the other types of treatment that we use: gold injections or bismuth. This child has not had a trial on these drugs.

Leprosy (Tuberculoid Type). Presented by DR. CHARLES SHEARD JR. for DR. JEAN CRAMER.

History:—J. L., a 26-year-old Cuban housewife, noted numbness of the right middle finger, with gradual swelling and pain in all joints of the hands and of both wrists. Similar swellings and numbness were noted in the left hallux. At this time she noted a plaque-like eruption of the arms and legs, with loss of sensation in the involved areas. Rash would become quite red and swollen from time to time and then fade out. The patient came from Cuba three months ago, where she lived in an endemic area, but denies any direct contacts.

Family history: Mother—facial paralysis; sister—epilepsy.

After the onset of the eruption, various medications were given, including iodides, salicylates, and vitamins, without change in the disorder.

Examination.—Skin: irregular erythematous plaques, slightly scaly with an elevated margin, are noted on the arms and legs. These areas are hypesthesic, but show normal hair growth. Hypesthesia is also noted on some areas of skin not involved by eruption. Scattered areas of depigmentation are noted over the entire torso.

Joints: joints of hands and feet are slightly swollen and tender.

Laboratory Findings.—Normal: c.b.c., urine, BUN, FBS, liver function tests, total protein, A/G ratio. Negative: Wassermann; PPD, 1 and 2, EKG; stool guaiac, and studies for ova and parasites. Chest films, survey of long bones: negative.

Mycology: scales showed Microsporum furfur. Biopsy of nasal mucosa: negative for acid-fast bacilli (AFB). Nasal scraping: negative on two examinations. Histamine test: absence of flare in anesthetic areas. Skin scraping: no bacilli found. Lepromin test: 3 mm. nodule is seen one month after injection of lepromin. Blood extraction for AFB: said to be positive.

Biopsy.—The epidermis shows slight hyperkeratosis and some pigmentation in the basal layer. As before, focal areas of granulomatous reaction are evident throughout the corium. One area over the subpapillary portion is involved, but in general the areas tend to be fairly sparsely localized, especially around the hair follicles and adnexae and apparently some of the vessels. As before, the infiltrate consists of epithelial cells with some giant cells of that type. The periphery of foci shows a moderate number of lymphocytes. No necrosis is seen.

Course.—The patient continues to have joint pains. Hypesthesia persists, as do the skin lesions which occasionally become very erythematous and elevated. Thiamine hydrochloride, 50 mg. q.d., is being given. No specific therapy has been undertaken as yet.

DISCUSSION

DR. MARION B. SULZBERGER: In my opinion this case is clinically so characteristic that it would be an error to withhold the available modern treatment for this disease. Moreover, the treatment with sulfones is not particularly dangerous, and the patient's response to the specific therapeutic trial might well clinch the diagnosis.

DR. JACK WOLF: What do you suggest?

DR. MARION B. SULZBERGER: Thiazolylsulfone (Promizole) or sulfoxone (Diasone) or diaminodiphenilsulfone(D.D.S.), e. g., Promacetin (sodium 4,4-diaminodiphenylsulfone-2-acetyl-sulfonamide).

DR. JACK WOLF: How about streptomycin?

DR. MARION B. SULZBERGER: Another point is that in the large leprosaria, for example in Cuba, where Pardo Castello was good enough to take me several years ago, one can always

find patients with characteristic leprous lesions in whom examinations of nasal smears and other attempts to find the bacilli over periods of 5, 10, 15 years have always brought negative results. All leprologists who see such patients are still convinced that they have leprosy, on the basis of the epidemiology, the clinical and histologic picture, the course, and the response to treatment. It must be inferred that there are cases of leprosy in which it can be extremely difficult to find the bacillus in the nasal smears or even in the tissues. Thus the diagnosis of leprosy cannot be ruled out in the case here presented just because of great difficulty in finding the bacilli.

DR. CARL T. NELSON: Since this patient is presumably tuberculoid and since the lepromin reaction is positive, the prognosis is excellent without any treatment. I don't see why you do anything but observe this patient.

DR. FRANK E. CORMIA: I disagree with Dr. Nelson on that last point. It is true that in some patients tuberculoid leprosy apparently does not progress over long periods of time, but it is also true that in patients with this form of the disease with and without treatment the disease may progress and may become much worse. Associated nerve lesions become much severer. Finally, the disease may undergo transition to the lepromatous type. Wade and various authors in South America have shown that the transformation from the tuberculoid to the lepromatous form of the disease may occur even with treatment. I believe this patient should be treated.

DR. ORLANDO CANIZARES: There is no doubt in my mind of the need of treatment for this patient. It is true that the tuberculoid type of leprosy is the benign form of the disease, but it is benign only in comparison with the lepromatous type. The neuritic forms, the changes of the hands, and the perforating plantar ulcers occur in this type. It is my opinion that the diagnosis is correct. The fact that the bacteriological examination was negative does not prove that the diagnosis is incorrect, as this is the rule in the tuberculoid type of leprosy, as in other diseases, such as tuberculosis. The diagnosis of leprosy is made by a combination of clinical, bacteriological, pathological, and immunological characteristics. Dermatologists are better equipped to diagnose the disease, as they can properly evaluate and interpret all these factors.

As far as treatment is concerned I think that any of the sulfones would be effective, by preventing progress and eventually arresting the disease. 4-4-Diaminodiphenilsulfone is now being used widely abroad because it is effective and inexpensive.

DR. JOSE MAY, Montevideo, Uruguay: I wanted to point out more or less what Drs. Sulzberger and Canizares have said; that is, that you do not have to find the bacillus to make the diagnosis of leprosy. It is very common to find the disease in patients in whom it is impossible to find the bacillus.

I should also like to point out the fact that treatment with isoniazid may have a favorable effect because the disease is of short duration. In some cases there may be such a favorable response that patients may recover their sensitivity.

DR. CHARLES SHEARD JR.: There was doubt whether the lepromin test was positive. We have the fear this may become the lepromatous type in the future. Therefore, we will, with your consent, treat the patient.

Ulcerative Lymphangioma in a Patient with Polycythemia Vera. Presented by DR. JOHN W. DOUGHERTY for DR. WORTHINGTON.

History.—F. R., a 51-year-old white man, a waiter, with known polycythemia vera since 1946, controlled by periodic phlebotomies and spray x-ray therapy, developed about three months ago a painless lesion on the medial border of the right nostril. The lesion grew rapidly to 1 cm. in diameter within three to four weeks. He was admitted at Polyclinic Hospital for excision. Bleeding was described as profuse. About three weeks later the lesion recurred and is still growing.

Examination.—The skin in general shows a slight dusky red hue, most noticeable on the legs. On the medial border of the right nostril there is a 4 mm. raised, raspberry-like, soft lesion.

Laboratory Findings.—9/15/53. *RBC, 8,700,000; Hgb, 134%*

Biopsy: Polypoid mass of tissue partially lined by squamous epithelium, partially denuded, with mononuclear and polynuclear cell infiltrate. Subepithelial tissue shows many spaces filled with pink-staining amorphous lymph fluid and lined with a flattened endothelial lining.

Diagnosis: ulcerative lymphangioma with subacute inflammation. (Biopsy report from Polyclinic Hospital.)

Course.—Since recurrence, the lesion has been treated only with neomycin ointment to control secondary infection.

DISCUSSION

DR. FRANCES PASCHER: On clinical grounds I should consider this an angiomatous lesion rather than lymphangioma. Patients with polycythemia vera may have more and larger angiomata at a commensurate age than normal persons. This patient also has a number of angiomata on the chest. These angiomata may be a part of the picture of polycythemia vera, a manifestation which has been described by Wiener in his textbook (Wiener, K.: Skin Manifestations of Internal Disorders, St. Louis, C. V. Mosby Company, 1947, p. 546.).

DR. EUGENE F. TRAUB: Since a pyogenic granuloma clinically would resemble the presenting lesion in this case, I should like to ask the presenter to explain how this diagnosis can be excluded, even taking into consideration the histology recorded.

DR. JOHN W. DOUGHERTY: It is a good question. The recurrence of the lesion first appeared, according to the patient, along the suture line. It was excised in another hospital. The biopsy report that you see is from another hospital. The question of pyogenic granuloma did come up. However, we went along with the pathologic report from the other institution. When we remove the lesion, we will run it through the laboratory and let you know.

DR. GEORGE M. LEWIS: While the history would support a diagnosis of pyogenic granuloma, the appearance is decidedly against that diagnosis. It is a dry, nonexudative lesion and dull red, rather typical of angioma.

Addendum: The histologic diagnosis was infected angioma.

Case for Diagnosis: Dermatitis Medicamentosa? Infectious Mononucleosis? Lymphoma? Erythema Multiforme? Presented by DR. JEFF DAVIS for DR. WORTHINGTON.

History.—A. M., a 30-year-old white postal carrier, developed an aching sensation in the ankle, knee, elbow, shoulder, and finger joints about five weeks ago. This was accompanied by dull epigastric pain, relieved somewhat by eating. His physician prescribed pentobarbital (Nembutal) elixir and belladonna, and the pain disappeared. One week later the generalized, pruritic, erythematous rash developed, and it has persisted to the present. There was an accompanying conjunctivitis and urinary frequency without urgency or urethral discharge. The patient stated he had a temperature of 100 to 101 F. daily. There was a 30 lb. (13.6 kg.) weight loss in the past two months, but he states he was on a voluntary diet. Past history includes discharge from the Navy for anxiety neurosis and a back injury in 1950 with a "slipped disc."

One brother died at the age of 37 of diabetes.

Examination.—Over the face, neck, trunk, and extremities is a patchy, erythematous, macular eruption, which fades on pressure. The conjunctivae are severely infected. There is no adenopathy.

Laboratory Findings.—9/24/53. Serologic test for trichinosis: negative. Urinalysis on two occasions: normal

9/15/53. Hemogram:

Hgb	14.5 gm. per 100 cu. cm.	Lymph.	33%
WBC	6,700	Mono.	3%
RBC	4,960,000	Eos.	1%
		Bas.	0
		PMN	58% mature 5% bands

Mazzini, negative

Total protein: 7.1; A/G: 4.7/2.4

Stool: no ova or parasites

X-Ray of chest: Negative

X-Ray of back: Not yet reported.

Heterophile agglutination: 1:28

Biopsy: None.

Course.—The patient has had a low-grade fever during the course of the present illness. While he was undergoing the work-up, the only drugs administered were antihistamines, and later kaolin with pectin (Kaopectate) with neomycin for two days for diarrhea. The latter cleared, and the antihistamine therapy relieved the pruritis.

DISCUSSION

DR. MAURICE J. COSTELLO: The only drug that I know of that produces so-called bloodshot eyes such as this patient presents is sulfathiazole, and I think that should be considered, although I questioned him about that and he said he did not receive sulfonamide drugs. But the eyes alone (the so-called bloodshot eyes) without accompanying inflammation point to sulfathiazole intoxication.

DR. JEFF DAVIS: Dr. Costello has seen many of these cases. We are interested in his opinion. There is no drug history of sulfathiazole. It has been a considerable length of time since we first saw the patient and since he has had any drugs at all that we know of. We should think that in the period of time that has elapsed if it were a drug the condition would be improving. Actually we think it is somewhat worse than when we first saw him.

DR. MAURICE J. COSTELLO: He is not using nose drops?

DR. JEFF DAVIS: No.

Incontinentia Pigmenti. Presented by DR. GEORGE M. LEWIS for DR. JEAN CRAMER.

Case for Diagnosis: Riehl's Melanosis? Poikiloderma Reticulare (Civatte)? Postdermatitic Pigmentation? Presented by DR. ANTHONY C. CIPOLLARO for DR. WORTHINGTON.

Lipid Dystrophy (Type?). Presented by DR. JOHN W. DOUGHERTY for DR. JEAN CRAMER.

Primordial Dwarfism; Discoid Lupus Erythematosus. Presented by DR. DOUGLAS P. TORRE for DR. JEAN CRAMER.

Leprosy (Tuberculoid Type). Presented by DR. CHARLES SHEARD JR. for DR. JEAN CRAMER.

Case for Diagnosis (Mycosis Fungoides?). Presented by DR. ANTHONY C. CIPOLLARO for DR. W. J. SCHMIDT.

Ulcerative Lymphangioma in a Patient with Polycythemia Vera. Presented by DR. JOHN W. DOUGHERTY for DR. WORTHINGTON.

Case for Diagnosis: Dermatitis Medicamentosa? Infectious Mononucleosis? Lymphoma? Erythema Multiforme? Presented by DR. JEFF DAVIS for DR. WORTHINGTON.

Alopecia with Myxedema. Presented by DR. DOUGLAS TORRE for DR. GEORGE SIMPSON.

Dermatitis Herpetiformis with Parasitophobia. Presented by DR. JEFF DAVIS for DR. W. J. SCHMIDT.

Recurrent Cellulitis of Legs—Etiology? Presented by DR. DOUGLAS TORRE for DR. GEORGE SIMPSON.

Sporotrichosis, Treated. Presented by DR. GEORGE M. LEWIS for DR. WORTHINGTON.

Lichen Sclerosis et Atrophicus. Presented by DR. ANTHONY C. CIPOLLARO for DR. WORTHINGTON.

J. Lowry Miller, M.D., *Chairman*

Timothy J. Riordan, M.D. *Secretary*

Nov. 4, 1953

All the cases presented at this meeting were from the Department of Dermatology and Syphilology of the New York University Post-Graduate Medical School and the Skin and Cancer Unit of the New York University Hospital.

Acrodermatitis Enteropathica. Presented by DR. DAVID BLOOM (Service of Dr. Nathan Sobel. Previously presented at The Manhattan Dermatological Society on Oct. 13, 1953, and the Bronx Dermatological Society on Oct. 15, 1953).

N. M., a boy aged 4 years, born in Italy and residing one month in the United States, was seen for the first time at the New York Skin and Cancer Unit on June 5, 1953.

Present History.—He presented then over the Achilles tendons, the ankles, the plantar surface of the toes, in the popliteal spaces, on the knees and elbows, on the arms and forearms, in the intergluteal fold and adjacent areas of the buttocks, and on the distal part of the penis fairly well definied erythematovesicular scaly plaques. There were also satellite vesicopustules present on the feet. Perlèche and blepharitis were present. All the fingers and toe nails had brownish discoloration, were thickened and distorted, with associated with severe paronychia.

The buccal mucosa showed reddish and whitish spots, and the tongue was covered with white fur. The entire scalp had thin fuzzy hair, and the eyebrows were thin, particularly in the lateral aspects.

Past History.—The following history was obtained from the parents: the boy was born at full term, delivered by a midwife. Two days later he developed convulsions, which were considered due to intrapartum cerebral hemorrhage. The convulsions never recurred. At the age of 3 months perianal and intergluteal erythema appeared, which lasted for about three months and reappeared several months later. At the age of 1 year after an attack of whooping cough and measles the eruption became exacerbated and gradually involved other skin areas and the nails. The hair on the scalp, which was present at birth in the form of a little fuzz and had grown only a little in the center of the scalp and in the occipital area, fell out at the end of one year and has consisted since then of a thin fuzz over the entire scalp.

At about the age of 6 months the child developed periodically, every four to eight weeks, diarrhea with four to five daily bowel movements associated with abdominal discomfort, anorexia, and apathy. These intestinal attacks were associated with exacerbation of the eruption on skin and oral mucosa. The tongue became covered and there was marked halitosis.

Family History.—The family history revealed that the parents are first cousins through the maternal side and that a younger sister, aged 2 years, is perfectly well. No other member of the family was affected.

Course.—During the course of our observations, we noted these exacerbations and remissions. During the exacerbations, the erythematovesiculobullous eruption on the feet became so severe that the patient had great difficulty in walking. His sad appearance and apathy during such attacks changed to cheerfulness during remission. In the periods of remission the plaques became drier and appeared hyperkeratotic and exfoliating.

Laboratory Examinations.—The blood cell count showed as the only abnormality relative lymphocytosis of 48%. The erythrocyte sedimentation rate was increased to 42 mm.

Mycological examination of the skin lesions revealed Candida albicans at the angles of the mouth, in a pustule on the foot, and in the nails; but the other skin lesions and the tongue did not yield any Monilia. In one pustule there were found in addition to C. albicans many colonies of staphylococci on subculture.

The fasting blood sugar was at one occasion 30 mg. per 100 cc., at another occasion 60 mg. per 100 cc., and the sugar tolerance curve was normal. Intradermal test with oidiomycin was positive to 1:1,000 but negative to 1:10,000 dilution.

In the feces, cysts of Giadia lamblia were found, but no Monilia.

Biopsy from a vesiculobullous lesion on the hand showed intraepidermal vesicles with marked inflammatory reaction of the papillary bodies. The upper cutis showed an infiltration of round cells and wandering connective tissue cells.

A biopsy from an erythematous plaque on the leg showed an increased granular layer and diffuse thin keratosis. In the cutis the blood vessels were enlarged and filled with erythrocytes. The upper cutis showed a mild cellular infiltration consisting of round cells and wandering connective tissue cells.

Treatment.—The first treatment, which consisted of application of antibiotic ointment and potassium permanganate baths, was of some benefit. But only since administration of diiodohydroxyquinoline (Diodoquin) on Aug. 29, 1953, first in the dosage of 210 mg. twice a day, has definite improvement been noted. In addition, methylrosaniline chloride, 2% in alcoholic solution, was applied to the lesions. It was found necessary to increase the dosage of diiodohydroxyquinoline to three times a day, and soon after to four times a day (Sept. 9). Methylrosaniline chloride was changed to iodochlorhydroxyquin (Vioform) cream.

Since about seven weeks ago the eruption has disappeared, and only dry mildly red erythematous plaques are left. The attacks of diarrhea have also ceased. The hair on the scalp has become thicker.

The following examinations were performed and found normal: complete blood count and blood chemistry—calcium phosphorus, nonprotein nitrogen, blood sugar, albumin/globulin; roentgenogram of g.i. tract and of chest; lipid partition of feces and examination for pathogens.

DISCUSSION

DR. BEATRICE M. KESTEN: We are indebted to Dr. Bloom for this remarkable example of acrodermatitis enteropathica. It has every feature described by Dillaha, even to the holding of the head on one side. I wonder, though, if all patients with acrodermatitis enteropathica have moniliasis. What is the relationship between the persistent moniliasis beginning in infancy and acrodermatitis enteropathica? We have a 14-year-old patient with similar skin lesions since infancy. Moniliae abound in the gastrointestinal tract as well as on the skin. Following Dr. Rothmann's suggestion, we gave diiodohydroxyquinoline for six months. No improvement was noted. It is my impression we had two distinct entities, (1) acrodermatitis enteropathica, and (2) moniliasis of the gastrointestinal tract and skin, occurring in infancy and persisting in poor protoplasm throughout life.

DR. HELEN CURTH: I wanted to ask Dr. Bloom if he considers a genetic background to the disease in this case, in which there is consanguineous marriage between the parents of the child.

DR. EMORY LADANY: I wonder if these lesions were at any time keratotic. When I saw these slides, it occurred to me that some of these lesions certainly looked very much like those seen in keratosis blennorrhagica. Considering that in Reiter's disease diarrhea and enteritis are often present as well as occasional keratotic lesions of the skin, I wonder if there might be some similarity in the pathogenesis of acrodermatitis enteropathica and Reiter's disease.

DR. PAUL GROSS: The distribution of the lesions is similar to that of widespread lesions of pellagra due to friction and tensile strain. This Koebner phenomenon is characteristic of skin manifestations due to disturbed cellular metabolism. The clinical experience with cases of acrodermatitis enteropathica would bear out the presence of a tissue deficiency which makes these patients more susceptible to infection with Candida albicans. Diiodohydroxyquinoline may act by changing the bacterial flora of the intestinal tract and thus improve vitamin synthesis. Certainly the therapeutic result that Dr. Bloom achieved is remarkable.

DR. FREDERICK REISS: I wonder what Dr. Bloom's answer is to the action of diiodohydroxyquinoline on Monilia infections. As far as I know, this drug has very little effect in systemic moniliasis. However, I know that Giardia lamblia is definitely affected by diiodohydroxyquinoline. Two organisms have been mentioned as being associated with the enteric infection. Which one was the cause of the acrodermatitis?

DR. FRANK C. COMBES: I am interested in Dr. Ladany's remarks on the resemblance of the eruption in this patient to that occurring in Reiter's disease. I do not agree that there is any particular clinical resemblance, but I do think that acrodermatitis enteropathica and Reiter's disease are pathogenetically quite similar. You know how I feel about these chronic toxic bullous dermatoses. I think they all arise from remote foci of infection, especially in the gastrointestinal tract, their clinical differences depending on the immunologic response of the patient at that time. This variation may cause Reiter's dsease at times to resemble even Duhring's disease, benign pemphigus, acrodermatitis continua, or generalized pustular psoriasis. I doubt the responsibility of Monilia as the organism in this patient. It is a common organism and may be a secondary invader. Like Dr. Reiss, I cannot understand how diiodohydroxyquinoline would affect a Monilia infection, nor can I understand the exact method by which it would act, as it is not absorbed to any appreciable degree. It is more logical to assume that diiodohydroxyquinoline destroys some other organism in the bowel, as any activity it possesses would of necessity have to occur in this organ.

DR. DAVID BLOOM: The fact that one does not find Monilia in the stools of these patients speaks against moniliasis being a primary factor. In this patient Monilia organisms were also not found in the mouth lesions. In Dr. Hopkins' case the skin lesions did not grow Monilia organisms, and they were considered by him as moniliids. Of 40 cases of moniliasis reviewed in the literature only three had the combination of symptoms found in acrodermatitis enteropathica.

Although our patient gave a skin reaction to a 1 : 1,000 dilution of oidiomycin, and a strongly positive complement fixation test to an extract of Candida albicans was obtained by Dr. Charles Rein, we considered the monilia infection in this child as secondary.

Of the 20 cases in the literature enumerated by Dr. Dillaha and collaborators (*J.A.M.A.* **152**:509 [June 6] 1953) 7 had familial occurrence. Our patient may be considered as the eighth case, for the fact that his parents are first cousins is a criterion for heredity.

This symptom complex has nothing to do with Reiter's disease. The keratotic lesions of which Dr. Ladany speaks are psoriasiform plaques into which the vesiculobullous plaques change in the course of involution or remission. The finding of Giardia lamblia in the stools I consider of no pathogenic importance, as this protozoon is thought to be a saprophyte.

The dramatic action of diiodohydroxyquinoline cannot be explained with certainty. However, if one wishes to speculate on the possible action of this drug, one has to do it in close connection with the conception of the acrodermatitis enteropathica syndrome. The following facts have to be considered: There are a number of cases which are unquestionably epidermolysis bullosa and which closely resemble this symptom complex, like the cases of Guy and Wende. Epidermolysis bullosa, particularly the dystrophic type, is considered, and justly so, as a congenital metabolic disturbance. The eruption in acrodermatitis enteropathica resembles, considerably at times, epidermolysis bullosa. It seems to me, therefore, not far-fetched, to consider acrodermatitis enteropathica related to epidermolysis bullosa. It may be conceived as a congenital metabolic disturbance of obscure nature producing gastrointestinal dysfunction which leads to involvement of the skin. Diiodohydroxyquinoline would have an effect on the gastrointestinal tract, neutralizing, let us say, the toxins in the gastrointestinal tract and thus preventing them from invading the skin. The alopecia of the scalp can be considered as due to the same toxic effect from the gastrointestinal tract as the skin lesions.

Case for Diagnosis: Pityriasis Rubra Pilaris(?). Presented by DR. SAMUEL B. FRANK (Service of Dr. Jesse A. Tolmach).

History.—The patient, J. C., a white boy, aged 15, was first seen at the Skin and Cancer Unit on Aug. 5, 1953, with a history of an eruption present three weeks. When the patient was first seen, he presented a widespread, discrete and confluent, flat, scaly, erythematous papular eruption involving the entire body, but with the greatest number of lesions on the upper trunk and neck. The lesion presented a Koebner phenomenon, with small papules on long scratch areas as long as 3 in. (7.6 cm.). The papules were about 2 to 4 mm. in diameter. While the patient was under observation, the character of the lesions changed. The isolated lesions became confluent, leaving an exfoliative picture in their place. The lesions on the forearms and hands and lower extremities became larger and have ultimately become stationary at approximately 1 cm. in diameter. The entire face and upper trunk developed exfoliative lesions with occasional clear areas of normal skin interspersed. Most of these clear areas are now gone. There are also lesions on the dorsa of the hands and fingers.

Laboratory Work-Up. 8/5/53—Serologic tests for syphilis were essentially negative except for a 1+ reaction on the Kline exclusion test. The other tests were negative.

9/18/53—Mycologic examination for fungi proved negative both microscopically and culturally.

8/10/53—Biopsy report: "There is a thick parakeratotic horny layer. The epidermis is regularly acanthotic. The basal margin is intact. The upper cutis shows a mild purely perivascular banal inflammatory reaction."

Microscopic Diagnosis: No evidence of lichen planus.

10/2/53—Biopsy report: "There is a thick parakeratotic horny layer. The epidermis is mildly and rather regularly acanthotic. The upper cutis shows mild perivascular inflammatory reaction."

Microscopic Diagnosis: There is no evidence of psoriasis or lichen planus. Pityriasis rubra pilaris cannot be excluded.

Therapy.—Vitamin A, 50,000 units, t.i.d.; petrolatum to the face. Zincundecate (Desenex) ointment was used on the left forearm with no apparent effectiveness.

DISCUSSION

DR. FREDERICK REISS: One of the most typical effects of pityriasis rubra pilaris is nutmeg grater-like lesions on the dorsal aspect of the first phalanges. In this case nothing of that is visible. Besides that, I failed to see palmar hyperkeratosis and the usual scaliness of the scalp associated with the disease. The Koebner phenomenon and the histopathological picture, however, are very suggestive that this boy may have psoriasis and that the process which we have seen today is a very mild type of psoriatic erythroderma.

DR. CHARLES WOLF: I will be very concise and say I think it is a case of psoriasis with a secondary exfoliative dermatitis. I would like to suggest to the presenter that this child be given a fat-free diet and a course of lipotropic substances internally, and that he be shown again next month. I think a startling involution of the lesions will be seen, if a rigid fat-free diet is carried out.

DR. PAUL GROSS: I agree with the diagnosis as presented. There is rarely a case of pityriasis rubra pilaris that does not present psoriasiform lesions. The diagnosis does not depend on the presence of keratotic plugs on the dorsum of the fingers, nor does the keratoderma of the palms occur in every case. I suggest that the treatment of this patient should include, in addition to vitamin A, extensive use of liver injections, folic acid, and vitamin B_{12}.

DR. FREDERICK REISS: I have to make a further remark in regard to histopathology. The very early histopathology in pityriasis rubra consists of follicular hyperkeratotic plugs. Not only are they characteristic of this but follicular hyperkeratosis shows a laminated structure in the very early stages of the disease. In this instance there is nothing of that sort visible, so I don't think that this can be classified as pityriasis rubra pilaris.

DR. ARTHUR B. HYMAN: On purely histologic grounds there is no evidence whatsoever of psoriasis, so this can be reasonably excluded. Pityriasis rubra pilaris is a diagnosis that is much more difficult to make on histologic grounds and surely can here not be excluded. The points Dr. Reiss made are hardly sufficient to make a positive diagnosis. Moreover, in a young boy, with the follicles still not well developed, the plugging might understandably be absent, and that is why one does not here see the typical features on proximal phalanges. This boy today has quite a severe seborrhea-like eruption of his scalp, although a week or two ago he did not have it, and he is beginning to develop the map-like clear areas in between the affected ones, so I think the diagnosis of pityriasis rubra pilaris is probably correct. In vew of the fact that he is clearing without treatment, I am not in favor of the suggestion that he be put on a fat-free diet. He is a tall, lanky lad, and with the proposed fat-free diet he may dwindle away to nothing.

DR. JESSE A. TOLMACH: This is a most unusual eruption. Earlier in the course of the eruption there were some annular elements suggestive of lichen planus. Psoriasis was also considered here. Histologic examination has, however, not demonstrated psoriasis or lichen planus. The diagnosis of pityriasis rubra pilaris may be valid, but if so, it is an atypical manifestation of that disease. At the moment, I feel that this patient has either an unusual variant of one of the common skin diseases or we are dealing with an entity which has not yet been reported. This case requires further observation.

DR. SAMUEL B. FRANK: I agree with Dr. Tolmach's comments.

Periadenitis Mucosa Necrotica Recurrens. Presented by DR. NATHAN SOBEL and (by invitation) DR. WILLIAM D. ELLER.

History.—F. P., a man aged 40, was first seen at the Skin and Cancer Unit, New York University Hospital, on July 8, 1953, and presented painful punched-out ulcerative necrotic lesions of both buccal mucosae, the right side of the tongue, the pharnyx, and the lower lip. No lymphadenopathy was present. There was no history of any member of his family having a similar condition. Since January, 1951, he has beeen having constant exacerbations and remissions of the lesions. The lesions would break down, slough, heal, and recur mostly in other areas. However, the ones on the lip, tongue, and pharynx have recurred in the same areas. A biopsy was performed at the Methodist Hospital, and he was informed there was no evidence of neoplasm.

Laboratory Findings.—Examination of the blood showed 4,700,000 red cells and 8,950 white cells with 70% polymorphonuclears and 26% lymphocytes. The blood Wassermann reaction was negative. Smears taken from an ulcer showed pus and epithelial cells, Gram-positive and Gram-negative cocci, and no acid-fast bacilli. Mycologic examination of material from an ulcer was negative for fungi. Roentgenogram of the chest showed no abnormal findings.

Histopathology.—The report by Dr. C. S. Miller was as follows: "The epidermis is slightly acanthotic. The inflammatory reaction is essentially in the cutis. At both ends of the slide the entire cutis consists of new connective tissue matrix, in which there are round cells, wandering connective tissue cells, leucocytes, and occasional plasma cells. There are also

some new blood vessels in this new matrix. In the center of the cutis there is organized connective tissue, in which we have a dense inflammatory reaction consisting of many leucocytes, round cells and wandering connective cells. The diagnosis is granulation tissue: no definite histopathologic picture."

Treatment.—Before the patient was seen by us, he was treated with various gargles and antibiotics, including daily intramuscular injections of penicillin for one week and oxytetracycline (Terramycin) 250 mg. daily for one month, without help. At the Skin and Cancer Unit he has been treated with hydrogen peroxide gargles, chlortetracycline (Aureomycin) troches, and chlortetracycline capsules. At present he is applying a 1% hydrocortisone (Hydrocortone) ointment to the affected areas, using hydrogen peroxide gargles, chlortetracycline troches, and multivitamines orally and parenterally. In spite of the above therapy, although his condition seems to be improving, the lesions have persisted. The patient feels that the hydrocortisone ointment has been the therapy that has given him the greatest benefit.

This case has been previously presented at the Manhattan Dermatologic Society on Oct. 13, 1953.

DISCUSSION

DR. HELEN CURTH: I do not see any difference in the case presented tonight and those showing the oral lesions of Bechet's syndrome or aphthosis. In the histologic description of the case shown tonight no mention has been made of any gland. If one reads Sutton's original description, one finds a gland mentioned, but the pathological process took place around this gland; therefore, the name periadenitis. Sutton himself believed that the gland may have nothing to do with the pathogenesis of the disease. In addition, Sutton mentioned other authors in whose cases the oral lesions were associated with genital lesions. I believe if we keep the name of periadenitis mucosa necrotica recurrens we emphasize a feature which is not important or does not play any role in this condition and, on the other hand, we make it impossible to associate these lesions with manifestations in other locations where there are no glands.

DR. DAVID BLOOM: At one time in the course of observation the patient had typical apthae on the lower lip. I believe that this is a severe case of ulcerative aphthous stomatitis, which to me is synonymous with periadenitis mucosa necrotica recurrens of Sutton.

DR. WILLIAM D. ELLER: The only thing I have to say is that the history, location, and clinical character are indicative of periadenitis mucosa necrotica recurrens, and I cannot think of any other diagnosis that fits this clinical picture.

Mycosis Fungoides. Presented by DR. JACK WOLF.

L. B., a white woman, aged 62 years, is presented from the Skin and Cancer Unit with an eruption on the trunk and extremities. The patient stated that for the past 35 years she has had a pruritic eruption, which started on the forearms and gradually spread to cover the extremities and trunk. The cold weather appeared to produce more erythema in the lesions, while the warm weather decreased the erythema. Examination shows the upper extremities and the trunk are slightly erythematous and covered by small scales. The lower extremities are covered by larger scales, which form a geometric pattern. A violaceous oozing, infiltrated plaque, approximately 6 by 5 cm., is present on the right breast. A similar lesion is noted on the right side of the abdomen. On the left side of the abdomen there are grouped nodules each approximately 0.5 to 0.75 cm. in diameter each.

Laboratory Data: S. T. S., negative; urine, not remarkable.

Biopsy: Diagnosis consistent with mycosis fungoides. The description was as follows: "Considerable parakeratosis, no granular layer, rather irregular. Acanthosis showing scattered areas of spongiosis and exocytosis. There is a cellular inflammatory reaction limited to the upper cutis and somewhat concentrated around the vessels, consisting of small round cells, histocytes, fibroblasts and foreign body nuclei in a loose and edematous connective tissue stroma."

DISCUSSION

DR. JESSE A. TOLMACH: Was this eruption preceded by parapsoriasis?

DR. DAVID BLOOM: I do not think it is unusual for mycosis fungoides to last a long time. I have observed cases of mycosis fungoides which have lasted for almost 20 years.

DR. NATHAN SOBEL: I always remember the case Dr. Rosen used to talk about that he followed for very many years, more than 30 years, with a very typical psoriasis, and it also ended up with a mycosis fungoides.

DR. JACK WOLF: The 35-year-old eruption has more of the features of atopic dermatitis than of any other eruption. The patient presents none of the features of parapsoriasis, and we are obviously not dealing with mycosis fungoides complicating the long-standing parapsoriasis *en plaque*. The question that arises here is, "What relationship, if any, exists between the long-standing atopic dermatitis and the complicating mycosis fungoides?" Surely this combined occurrence is a rare one. Any opinion as to the etiologic relationship between these two dermatoses must remain purely conjectural.

Alopeca Universalis Treated with Oral Cortisone. Presented by DR. VICTOR H. WITTEN and DR. MARION B. SULZBERGER.

Past History.—Small patch of alopecia at the occiput, occurring at about the age of 6 years, in which the hair never regrew. Lost right eyelashes at age 14; these regrew soon afterwards.

Present History.—The patient, S. L., a 42-year-old white woman, was first seen on March 30, 1951. Approximately at the beginning of 1950 the patient noted sudden onset of loss of hair from the scalp, and the hair loss rapidly involved the extremities, the trunk, and lastly the eyelashes.

Examination.—At the time of examination on March 30, 1951, the patient had no hair growth anywhere on her body.

Previous therapy, including phenol paintings, grenz radiation, vitamins orally and by injection, hormones by injection and topically, sedatives, and the local injection of cortisone acetate, failed to produce any changes.

Course.—Cortisone therapy: On Jan. 3, 1952, patient was started on 100 mg. of cortisone acetate orally in divided doses daily. This amount was continued until Oct. 31, 1952, when it was reduced to 75 mg. daily. On March 27, 1953, the dose was reduced to 50 mg. daily, but had to be increased again to 75 mg. a day on April 10, because the remaining spots of alopecia were increasing in size and new ones were appearing. By May 14, patient was taking 150 mg. a day.

On June 2, hydrocortisone, 120 mg. a day, was given in place of cortisone. Since then the dose has been reduced gradually until the present. The current dose is 80 mg. of hydrocortisone a day. The steroid intake was accompanied by a low-salt diet and supplemental potassium in the form of potassium chloride.

Weekly checks of blood pressure and weight, together with urinalysis, did not show any deviations from the expected norm. Blood chemistry values, including sodium, potassium, and glucose, remained within normal limits.

Very recently the patient complained of a feeling of slight depression and weakness. A thorough physical examination, including laboratory work-up, revealed some impairment of adrenocortical function, as follows: decrease in mineralocorticoids, as manifested by muscle spasm and weakness, low blood sodium, and high serum potassium; decrease in androgenic steroids, as manifested by low 17-ketosteroid excretion. Corticosteroid activity (from exogenously administered hydrocortisone) was evidenced by: normal glucose- and insulin-tolerance tests; high 11-oxysteroid excretion.

DISCUSSION

DR. MAURICE J. COSTELLO: This is a remarkable example of the return of hair in a patient with alopecia universalis. For every patient who responds in this manner there are many who do not. I am more impressed by the result when it occurs in a patient who had had alopecia universalis for a period of five years. In my experience with alopecia universalis, cortisone and corticotropin (ACTH) are beneficial only temporarily. In and of itself it has no permanent beneficial effect.

DR. CARL T. NELSON: I think our experience at Vanderbilt Clinic has duplicated Dr. Costello's, but I wonder if we possibly have not carried out the treatment long enough. I

thought that eight weeks of cortisone, 100 or 150 mg. a day, would be sufficient. I should like to ask if Dr. Witten feels that one should continue this treatment for a longer period of time in each case before giving up.

DR. JUAN LARRALDE: It is not unusual to find cases of total alopecia improved with cortisone, but the point is how long does it last? It lasts only while the cortisone is being taken. I remember a case in the Kingsbridge Hospital in which the patient improved greatly under the treatment. As soon as the cortisone was stopped the hair began to fall again.

DR. RUDOLF L. BAER: I think that Dr. Rothman's original publication already pointed out that it is a very small minority of patients in whom an apparently "permanent" acceptable cosmetic result is produced with cortisone and corticotropin, and that such a result is maintained only if one continues with the medication. I don't think that it is very likely that the regrowth of hair in this patient presented here is just a coincidence, because some inadequate regrowth of hair is noted a few weeks after cortisone therapy has been started, even in some of the patients with alopecia totalis who have a poor result. I think that most of them show at least some regrowth of hair, even after they have been devoid of any hair for many years, a fact which one could not explain purely on the basis of coincidence. It appears then that while many patients with alopecia totalis have some, no matter how unsatisfactory, response to cortisone therapy, there is an extremely small percentage in whom the cortisone produces an excellent cosmetic result. I am sure that most of you have talked to alopecia totalis patients and know what a disastrous effect the alopecia has on their entire life. I see every justification for keeping these patients on this medication over a prolonged period of time.

DR. VICTOR H. WITTEN: The question of coincidence or response to treatment almost always occurs when regrowth of hair is noted in alopecia, regardless of its type. Dr. Nelson's question as to how long the hair will remain after the cortisone is discontinued can serve as a basis on which to answer Dr. Costello's criticism. When this patient's dose of cortisone was reduced to 75 mg. a day, her alopecia began to reappear. The hair fell out again in areas in which it had regrown under cortisone therapy. When the dose of cortisone was increased, the hair regrew. I would think that we all agree that if the drug were stopped or reduced below the maintenance dose, this patient would begin to lose hair once again. To answer the question as to how long one should give cortisone before seeing results: This patient did not have one hair on her body at the time treatment was started. It took four to six weeks before we saw profuse growth of lanugo hairs. These were noted along the top of the head and appeared before we could see eyebrows and eyelashes. It took many more weeks before a "worth-while" hair growth was noted. I, therefore, think it is necessary to treat longer than the eight weeks Dr. Nelson said they treated their cases.

As regards the dose, it must be individualized, just as doses of cortisone are individualized in other diseases. Whereas the protocol states that the patient was started with 100 mg. of cortisone a day, she actually received 150 mg. a day for four days, after which it was reduced to 100 mg. a day. Of course, in other cases the starting dose may necessarily be more or perhaps less. Our reason for giving the cortisone in this case and for maintaining it was not to see whether we could keep hair on the patient's head, but it was for the reasons mentioned by Dr. Baer. This patient was mentally at the lowest ebb, almost to the point of suicide. She already had seen a psychiatrist. Her will to make a living and her mood are apparently dependent largely upon the degree of hair regrowth. When she began to lose hair with the drop in cortisone dose she began to go into a depressed state again. We do not think this was because of the diminished dose of cortisone, as the depression followed the hair loss, not the dropping of the cortisone dose, between which there was a lag period of many days.

Extensive Keloid Treated with Thorium X Solution. Presented by DR. A. J. ORFUSS. (Service of Dr. Frances Pascher).

J. F., a woman, aged 40; Chart No. M 30261.

History.—In 1943 and in 1945 "cysts" were removed by surgery from the upper inner quadrant of the right breast. These operations were followed by progressive keloid formation on the operative site. The keloid grew larger, itched severely, and looked unsightly, so treatment was sought in March, 1951. History is otherwise noncontributory.

Physical Examination.—In 1951 the medial quadrant of the right breast presented an oval 11 by 6 sq. cm. uneven keloid, with alternate raised and depressed and contracted areas. The periphery was red, raised, thickened, and slightly excoriated.

Treatment.—The lesion was divided into four quadrants. One quadrant was treated with x-ray therapy (four treatments, one every three weeks, 255 r per dose, 100 kv., 5 ma., 20 cm. distance, no filtration, H.V.L. 0.9 mm. Al, with close shielding). One quadrant was treated with 6 CO_2 applications. One quadrant was treated with applications of thorium X solution in alcohol, every two weeks, 300 μc per cubic centimeter, five applications at each treatment, for six treatments. The last quadrant was left untreated as a control.

Careful evaluation resulted in the opinion that most progress had been made by the CO_2 and thorium X treated sites. Because of pain involved, further treatment with CO_2 was abandoned, and the entire lesion was then treated with thorium X solution applications for a total of 18, once every three weeks. The last treatment was given in March, 1953. The lower border of the lesion is still slightly thickened and red, but the entire sclerotic mass has softened, and itching has diminished.

DISCUSSION

DR. DAVID BLOOM: Was thorium X used in old or young keloids?

DR. PAUL GROSS: What is the optimal microcurie concentration for the treatment of keloids?

DR. MAURICE J. COSTELLO: This woman had, as was said before, treatment by various means, including solid carbon dioxide. What part of the keloid has been definitely affected favorably by the thorium X? I would like to know how often that had been applied and for how long and whether this has ever been used on other keloids. Certainly if it is as effective as it appears to be in this case, I imagine that we will all get on the bandwagon. From my experience a keloid is the most difficult lesion to treat, and it is amazing to think that a keloid, which under ordinary circumstances, is radioresistant is so radiosensitive to thorium, which has such superficial action.

DR. A. J. ORFUSS: The first question as to the different modalities that were used in treatment was answered in the protocol. A trial of six treatments with thorium X, the recognized dosage with x-ray, and six treatments with carbon dioxide were given to the three selected areas. We reevaluated the treated sites at the end of that time and found that the thorium X and the carbon-dioxide-treated areas responded best of all. We then proceeded to treat the entire lesion with thorium X. You can see that there is one area, the upper outer quadrant, which received nothing but thorium X, and the response in that area can be said to be completely due to the thorium X. The others were treated to some extent with x-ray or carbon dioxide.

We have treated keloids that were so old that they had reached the old sclerotic hard stage of this lesion. When we first started with it, this lesion was four years old; we have other similar cases. Some of the others did not respond as well as this. I must say this: I think this is an unusually good result.

The question with reference to the strength of the solution was referred to Dr. Witten, and I will ask him to answer that question. The solution that we used was 300 μc per cubic centimeter. Using 0.5 cc. we would be using half of the amount or 150 μc.

DR. MAURICE J. COSTELLO: I should like to get it clear before this group here as to how many lesions were so treated and how many were affected favorably, how many were affected unfavorably. It is very difficult for me to believe that six applications of thorium X, which will hardly clear up a patch of psoriasis which is radiosensitive, will clear up a keloid which is not radiosensitive. It just does not make sense to me, and I would like to know more about it.

DR. A. J. ORFUSS: The actual number of treatments that the keloid received was a total of 18; it was not a total of 6. We stopped at the end of 6 treatments to reevaluate, and then we added an additional 12 treatments so that the patient had a total of 18 treatments with thorium X to the entire keloid.

DR. MAURICE J. COSTELLO: The entire? I thought you said the lower quadrant.

DR. A. J. ORFUSS: The outer quadrant was the part first treated with thorium X. When we evaluated it, that was one of the quadrants that responded best of all, so we decided to treat the entire keloid, all four quadrants, with thorium X, to which we gave an additional 12 treatments.

DR. MAURICE J. COSTELLO: Another question: how many keloids have responded to thorium X and how many have not?

DR. A. J. ORFUSS: I think we have treated a total of about six.

DR. VICTOR H. WITTEN: Perhaps I should try to answer Dr. Costello's question in so far as my memory will serve me. A small keloid which followed injury on the wrist of a man was first treated with unfiltered x-radiation (3 treatments, each ¾ skin unit [255 r], given at three-week intervals). No response was noted even after several months' observation. We then used thorium X, with considerable flattening of the keloid. Approximately six treatments were given. A keloid almost the size of the one seen tonight on the back of a woman was also treated with thorium X. It, too, was divided into quadrants, each of which was treated differently, as described by Dr. Orfuss. In addition, four satellite keloids were treated by the same four modalities. Again the response to thorium X was considered favorable and it was selected to treat the entire lesion. A total of 15 to 18 treatments were given. Keloids on the midchest have not always responded well. I recall one that flattened about 50% in five treatments. Two other keloids of the chest failed to show any response at all. This was also true of several keloids which I recall on other areas. The method of application of the thorium X is important. We tackle them rather forcibly. The "old" blanched and sclerotic keloids become red again as though they were acutely inflamed.

DR. JACK WOLF: How often was the treatment administered?

DR. VICTOR H. WITTEN: Once every three or four weeks.

Benign Cystic Epithelioma of the Face. Presented by DR. JUAN LARRALDE.

E. R. is a Negro man, 21 years old, who was born in the Virgin Islands.

Family History.—Mother and grandmother had same lesions. None of his three sisters or one brother have any.

Duration and Description.—Present since birth, lesions have become larger lately. The forehead, upper eyelids, lateral corners of the eyes, and entire nose except the lip and upper tip are covered with conglomeration of pea-sized, skin-colored, soft papules.

Laboratory Findings.—Biopsy report: Multiple benign cystic epithelioma. Lesion shows several follicular cysts, from the walls of which arise differently shaped basal-cell proliferations containing nests of concentrically arranged cells showing elongated nuclei and acidophilic cytoplasm (hair matrix?). One also sees islands of basal-cell-like cells without connection with the follicles. At one point there is a basal cell mass of adenoid structure arising from thinned and flattened epidermis. The palisade layer is retained. The basal cell layer of the epidermis is pigmented. There is marked fibrosis around the cell masses. No inflammatory reaction is seen. The superficial blood vessels are dilated.

DISCUSSION

DR. TIMOTHY J. RIORDAN: I have never seen two cases presented at one meeting with such an extensive involvement of the face, and in both cases the involvement is so extensive that I would suggest that they be turned over to a plastic surgeon for a full skin, full face graft.

DR. BEATRICE KESTEN: If these lesions are benign, before the patient is turned over to the plastic surgeon, would it be all right to try planing?

DR. DAVID BLOOM: I believe that fulguration or dessiccation give good results, and I would prefer this treatment by far to plastic surgery. In Negro patients one has to try this treatment in a small area in order to see whether keloidal formation takes place.

DR. JUAN LARRALDE. Frankly, I don't agree much with the idea of a plastic surgeon in this case. I agree with Dr. Bloom and I believe we can try some electrosurgery, although from my experience that has been very poor most of the time. The lesions recur.

DR. EMORY LADANY: We presented this case solely for suggestions on therapy. I think we will try to base our therapy on a combination of all the suggestions, for which I thank the discussers.

Congenital Telangiectatic Erythema in a Levi-Lorain Dwarf. Presented by DR. DAVID BLOOM (Service of Dr. Nathan Sobel).

G. S., a white boy, consulted us for the first time in July, 1941, at the age of 9 years, for an eruption on the face which had been present since the age of two.

Physical Examination.—The child was small for his age. The face had peculiar babyish features. The voice was shrill. Examination of the skin showed erythematous telangiectatic plaques on the nose, adjacent parts of the cheeks, left upper eyelid, and forehead. The lower lip showed edema, crusting, and fissuring. On the trunk there were found a number of *cafe-au-lait* spots, a pilondial cyst, and hyperkeratotic hyperpigmented skin resembling ichthyosis hystrix in the axillary regions and on the flanks. On the left flank there was an irregularly shaped plaque of telangiectasia. There was marked lichen pilaris on the arms, abdomen, and thighs.

Family History and Past History.—No other member of the family was affected with dwarfism or any cutaneous abnormalities. The boy, a second-pregnancy child, was born at full term weighing 4 lb. (1,814 gm.). Because of his stunted growth, which was noticed a few years after birth, and which was considered due to pituitary hypofunction (Lorain-Levi dwarfism), the child was treated from the age of 4 years during several years with anterior-pituitary growth hormone. At the age of 5 years he suffered from acute mastoiditis and pyemia, resulting in numerous recurrent abscesses, causing ankylosis of the left ankle joint and shortening and thinning of the left lower extremity. Since about the age of 2 years erythematous plaques have appeared on the nose and face, and a bullous and crusted eruption on the lower lip; these were worse in summertime, particularly following sun exposure. In 1941 the patient was observed and treated for his dwarfism at the Pediatric Department of the University Hospital, at which time it was found that he was highly myopic. Roentgenograms at that time showed the bony structures of the skull to be small for his age. However, epiphyseal development of the bones was compatible with sex and age. An encephalogram revealed dilatation of the ventricles. The basal metabolic rate was on several occasions —18%.

Course.—The eruption on the face was diagnosed as lupus erythmatosus until a biopsy in 1952 showed only telangiectasia in the upper corium. The recurrent eruption on the lower lip and the exacerbation of the lesions on the nose were considered as due to solar sensitivity, but no uroporphyrin was found in the urine. Several courses of bismuth injections did not benefit the eruption at all, but electrolysis to the erythematous spots on the nose and face has resulted in the past year in improvement. Since the patient has avoided sun exposure no bullae have developed on the lower lip.

DISCUSSION

DR. BODIAN. Has the mentality of this child changed at all?

DR. DAVID BLOOM: There seem to be no mental changes in our patient.

Actinomycosis and Squamous Cell Epithelioma. Presented by DR. DAVID BLOOM and DR. D. GAMSAGER (From the Department of Dermatology and Syphilology of the New York University Post-Graduate Medical School and the Service of Dermatology and Syphilology of Bellevue Hospital [Dr. Frank C. Combes, Chief of Service]).

S. W., a 55-year-old white woman.

In January, 1953, the patient noticed a lump on the inner aspect of the right side of the mouth and an ulcer at the right angle of the mouth. A biopsy revealed actinomycosis and squamous cell epithelioma. Actinomyces bovis was observed on culture examination.

On Feb. 21, 1953, the patient was admitted to Bellevue Hospital, at which time physical examination revealed an ulcer at the right angle of the mouth, surrounded by a firm border. Purulent material drained from the base of the ulcer. There was a walnut-sized mass lateral to

the right angle of the mouth and attached to the skin and mucous membrane. There was also a pea-sized nodule at the right angle of the mouth, with a sinus opening in the center from which a purulent material could be expressed. In the right cervical region just below the ear there was also a lemon-sized firm tumor.

The actinomycosis was treated with 2 gm. of oxytetracycline (Terramycin) daily, 600,000 units of penicillin b.i.d., and 30 drops of potassium iodide t.i.d. The epithelioma at the angle of the mouth was treated with x-radiation consisting of three 300 r doses and eleven 392 r doses with 0.5 or 1 mm. filter. Both the actinomycosis and the epithelioma responded well to treatment.

The cervical node was aspirated several times and Actinomyces bovis was found each time. The tumor decreased in size but never disappeared completely. A biopsy of the cervical node was advised, but the patient refused to have it done.

The patient was discharged from the hospital on July 25, 1953, and did not return until Oct. 12, 1953, at which time the cervical tumor had enlarged to the size of a small orange and on the inner aspect of the right upper jaw and gum there was a necrotic area 2 by 3 cm. in size.

A needle biopsy of the cervical tumor was attempted, but only some blood-tinged purulent material was obtained, which will be examined for actinomycosis. A biopsy was taken from three areas inside the mouth on the right side. Further treatment will be decided according to pathological and mycological report.

Addendum: Pathology Department reported sections of right buccal membrane as squamous cell carcinoma via telephone.

DISCUSSION

DR. RUDOLF L. BAER: I want to call attention to the difficulties in some of these cases in making a histologic diagnosis. When this patient was originally presented I remember that one of the histopathologists seemed to feel that the prickle cell changes were pseudoepitheliomatous, and others thought they were a prickle cell epithelioma. The further developments have shown that those who said we were dealing with a prickle cell epithelioma were correct.

DR. ARTHUR B. HYMAN: I am sure among histopathologists there is agreement that the sections show epithelioma-like hyperplasia. There were some clinicians who thought this was purely a case of actinomycosis, and what the pathologists regard as malignant dysplasia was on clinical grounds interpreted by these clinicians as being pseudoepitheliomatous. I do not think that the clinician without histologic experience is in a position to contradict the pathologist when it comes to this question, and we are undoubtedly dealing with what was and is a prickle cell epithelioma.

DR. CARL T. NELSON: May I ask Dr. Hyman or Dr. Bloom how often actinomycosis and squamous cell epithelioma occur in association in the same patient?

DR. CHARLES S. MILLER: There were two sections of tissue submitted to the laboratory. The first was taken from the lip. It showed the epidermis intact and acanthotic. The cutis was occupied with masses of proliferating prickle cells. Histological diagnosis: Prickle cell epithelioma.

The second section consisted of cutis only. Within this cutis, there were similar masses of proliferating prickle cells.

These sections first came to me. I requested that they be shown to the other histopathologists at the New York Skin and Cancer Hospital. For the first time, all the histopathologists agreed. There were no differences of opinion, and that was quite an achievement at our hospital.

DR. DAVID BLOOM: In answer to Dr. Nelson, I found only five cases in the literature of actinomycosis associated with carcinoma. One biopsy taken at Bellevue Hospital from the angle of the mouth was reported by the general pathologist as an "atypical hyperplasia of the epithelium."

DR. D. GAMSJAGER. Observation of this patient and the laboratory findings lead us to believe that we are dealing here with two conditions, squamous cell carcinoma and actino-

mycosis. It is not quite clear why the cervical swelling has increased markedly in size in the course of several months following discharge from the hospital, for the aspirated pus did not grow any actinomyces and the wall of the cyst did not show any pathologic structure of cancer.

Tuberculosis Cutis. Presented by DR. FRANCES PASCHER and DR. NORMAN KANOF (by invitation).

Mycosis Fungoides (Treated with TEM [Triethylene Melamine] and Cortisone). Presented by DR. DAVID BLOOM and DR. GUTIERREZ.

Epidermolysis Bullosa. Presented by DR. FRANK C. COMBES.

Syringoma of the Face. Presented by DR. MAURICE J. COSTELLO and DR. ROGACHEFSKY.

Lichen Planus. Presented by DR. JESSE TOLMACH.

Pemphigus Vulgaris. Presented by DR. WILLIAM DIRECTOR and DR. ROGACHEFSKY.

Creeping Eruption (Larva Migrans). Presented by DR. WILLIAM DIRECTOR and DR. SILVERBERG.

Granuloma Annulare(?). Connective Tissue Nevus(?). Presented by DR. JACK WOLF.

Lichen Spinulosus. Presented by DR. KATE MILLER.

Lichen Sclerosis et Atrophicans? Foreign Body Reaction? Presented by DR. SAMUEL B. FRANK.

Pemphigus Vulgaris. Presented by DR. DAVID BLOOM (DR. BENDER and DR. D. GAMSJAGER by invitation).

Urticaria Pigmentosa. Presented by DR. JOSEPH L. MORSE.

Case for Diagnosis: (A) Lichen Planus and (B) Psoriasis. Presented by DR. JESSE A. TOLMACH.

Case for Diagnosis: Scleroderma (Localized Type)? Sclerodema Adultorm (Buschke)? Dermatomyositis? Erythema Type? Presented by DR. MAURICE J. COSTELLO and DR. JIRAYR TEZEL.

Trichoepithelioma. Presented by DR. EMORY LADANY and DR. JIRAYR TEZEL.

Periadenitis Mucosa Necrotica Recurrens. Presented by DR. NATHAN SOBEL and (by invitation) DR. WILLIAM D. ELLER.

Obituaries

WILLIAM HARVEY GUY, M.D.
1887-1953

Dr. William Harvey Guy died on Nov. 13, 1953, after a lingering illness. Dr. Guy was born in Holt, Pa., on March 24, 1887. He received his preliminary education in the public schools in Pittsburgh. He was graduated from the University of Pittsburgh Medical School in 1910. The following year he interned at Allegheny General Hospital, following which he engaged in general practice for a few years on the Northside of the city. He received his dermatological training at the Vanderbilt Clinic in New York City, of which Dr. John A. Fordyce was chief. Dr. Guy served chiefly under the direction of Dr. George M. MacKee, in whose office he practiced until his enlistment in the Army in World War I. On April 23, 1919, he was discharged from service at Camp Travis, Texas, with the rank of Captain. He returned to Pittsburgh to enter the practice of dermatology, where he continued until his death. In 1920, he was appointed head of the Department of Dermatology at the University of Pittsburgh Medical School, in which position he continued until 1951. For the past two years he served in the capacity of Professor Emeritus.

Dr. Guy served as secretary and chairman of the Section on Dermatology and Syphilology of the American Medical Association and as secretary and president of the American Dermatological Association. He was a past president of the Allegheny County Medical Society, a member of the Pittsburgh Academy of Medicine and the Medical Society of the State of Pennsylvania. He was chief of dermatology of the various hospitals at the University of Pittsburgh Medical Center, and of Allegheny General and South Side hospitals, where he served until his retirement two years ago.

Dr. Guy will be remembered for many valuable contributions to dermatological literature, but will be remembered most by his many friends who knew him as a kindly advisor, a great teacher, and a friend to whom they always could turn for help. To his many intimate friends his great wit and ability to recount experiences and tell stories will be a long-cherished memory. Throughout his entire medical career he was an ardent devotee at the altar of Hippocrates. His death was a great loss to the dermatological profession, which held him in highest esteem.

He is survived by his widow, Dorothy Hunt Guy; his son, Dr. William B. Guy; his sister, Miss Eula Guy, of Beverly Hills, Calif., and three grandchildren.

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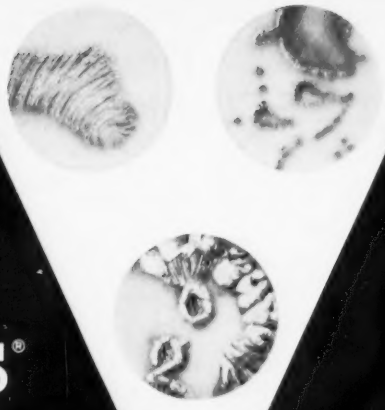

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References:

1. Ellis, C. C., and others: The Treatment of Psoriasis with Liquor Carbonis Detergens, J. Invest. Dermat. *10*:455, 1948.

2. Sulzberger, M. B., and Wolf, J.: Dermatology, Essentials of Diagnosis and Treatment, Chicago, Year Book Publishers, Inc., 1952, p. 323.

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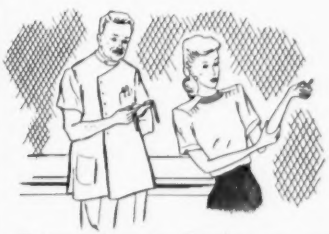

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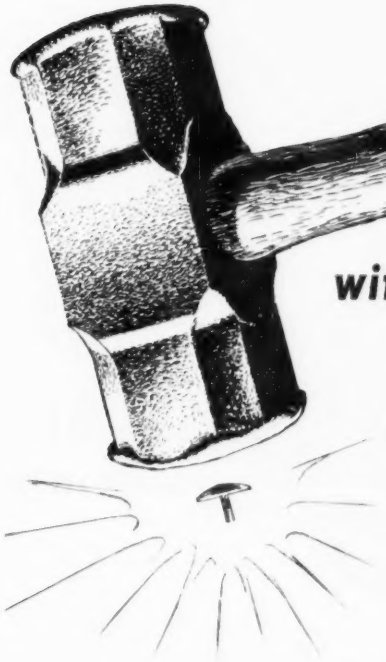

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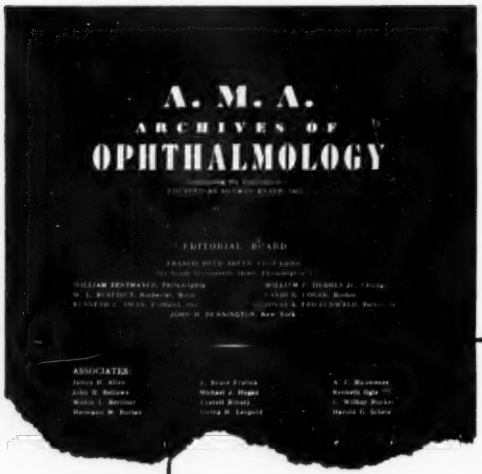

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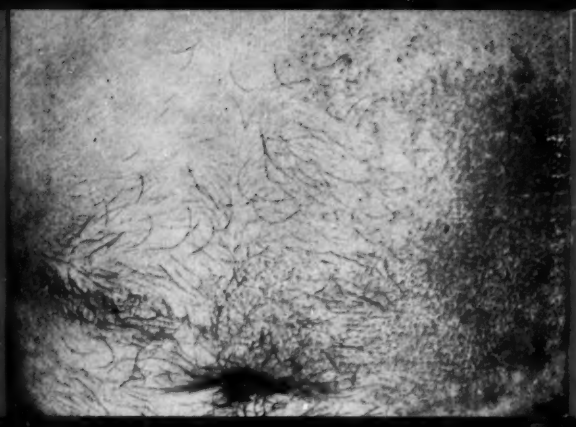

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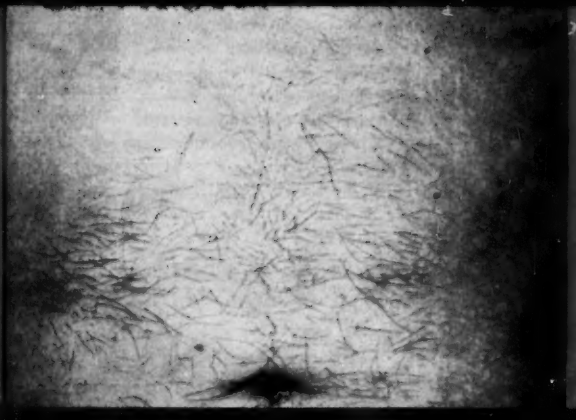

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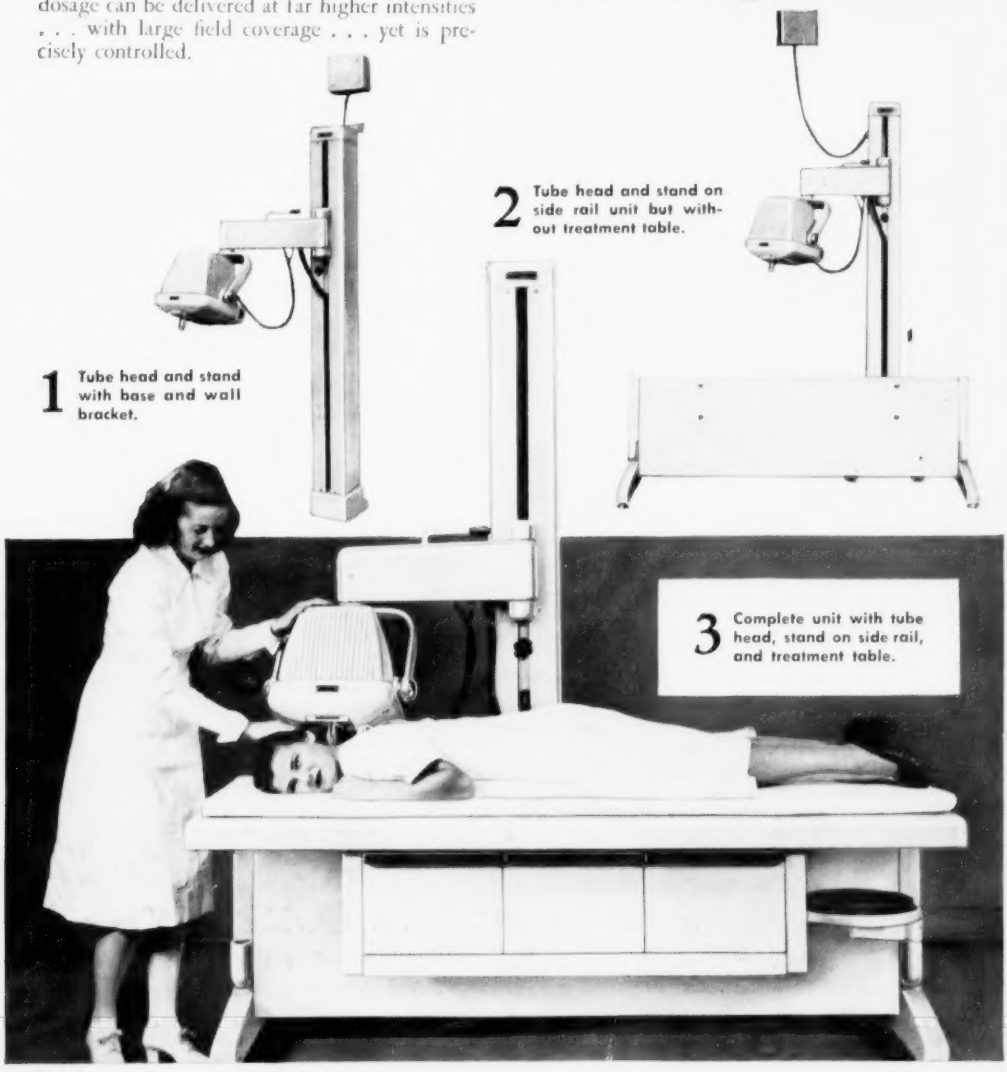

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